Appendix D
EPA Region 5 Recommended Avian and Mink PCB Toxicity Reference Values

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
REGION 5

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SUBJECT: Toxicity Reference Values (TRVs) for Mammals and Birds Based on Selected Aroclors

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1 Summary

Toxicity reference values (TRVs) are developed for polychlorinated biphenyl (PCB) mixtures based on studies of controlled exposures to commercial Aroclor products for sensitive mammal (mink) and bird (chicken) species. The TRVs are interpolated from dose-response plots of Aroclor exposure and reproductive or growth endpoints, with data collated from multiple studies. The interpolated low-effect level is the dose that results in a 25 % decrease in an endpoint response compared to that of the control group, and the interpolated no-effect level a 10 % decrease.

The TRVs are recommended for mink or conservative application to bird species that lack species-specific PCB toxicity data. Since the TRVs are derived from studies of sensitive species to PCBs, use of uncertainty factors for extrapolation to other species is not recommended. The TRVs are given as bodyweight normalized doses (mg PCB per kilogram bodyweight per day) for ingestion by birds to facilitate application to bird species of different sizes. Dietary TRVs (mg PCB per kg food) on a wet weight (ww) basis are given for mink since interspecific extrapolation is not necessary to assess risk to wild mink. The TRVs for bird eggs are given as the concentration in whole eggs on a wet weight basis (mg PCB per kilogram egg).

The TRVs are summarized in Table 1. See the text for details.

Table 1. Interpolated PCB Toxicity Reference Values (TRVs) Based on Controlled Exposures of Mink and Chicken to Commercial PCB Products.

Commercial PCB Product (Aroclor)	Mink Diet [a]		Bird Dose		Bird Egg	
	mg/kg ww		mg/kg_{BW}-d		mg/kg whole egg ww	
	no effect	low effect	no effect	low effect	no effect	low effect
1242	1.3	1.4	0.1 - 0.5 [b]	0.4 - 0.8 [b]	1.0	1.5
1248	see 1254 [c]	see 1254 [c]	0.4	0.5	0.7	1.3
1254	0.5	0.6	0.6	1.2	9	12

Notes for Table 1:

a) Mink TRVs are adjusted for continuous exposure over multiple years or generations at the same site (see text).

b) Two response patterns are exhibited in the published studies, which are separately assessed (see text).

c) A1248 has not been tested in mink. The mink A1254 TRVs are applied because A1248 is as potent as A1254 in an *in vitro* mammalian bioassay (Tillitt, et al. 1992).

The TRVs for mink are adjusted for continuous exposure through two breeding seasons or generations because mink feeding studies with one of the European commercial PCB formulations (Clophen A50) and, independently, with field-contaminated fish have shown pronounced increases in toxicity compared to exposure over a single breeding season. The A1254 TRV is based on the number of live kits per mated female and kit bodyweight at birth. Although kit survival following birth might be a more sensitive endpoint compared to live kit production or kit bodyweight at birth (see Clophen A50 below), the data are insufficient for determining kit survival TRVs for A1254, other than to state that the low-effect dietary concentration is less than 1 mg/kg for a single season of exposure. Surprisingly, no mink feeding studies were located for A1248. However, A1248 is as potent as A1254 in an *in vitro* [1] mammalian bioassay (Tillitt, et al. 1992), so the A1254-based TRVs are applied to A1248. The TRVs for A1242 are based on live kit production. Data are insufficient for other endpoints for A1242.

For comparison, the mink dietary TRVs for Clophen A50, one of the European commercial PCB products, over 2 seasons exposure are 1.1 to 1.3 mg/kg for live kit production (no effect to low effect), 2.3 mg/kg for kit bodyweight (low effect), and less than 0.8 mg/kg for kit survival (low effect). Data are insufficient to determine no effect TRVs for the latter two endpoints, other than to state that the no effect TRVs are greater than the control dietary concentration of 0.01 mg/kg.

All of the TRVs from chicken studies are based on hatchability, the most frequently reported endpoint of PCB studies with chicken. Chick bodyweight is a less sensitive endpoint in the few cases for which comparisons can be made with hatchability. Chick survival appears to be a more sensitive endpoint than hatchability in the sole available comparison (low effect TRV of 0.3 mg/kg_{BW}-d for A1248), but is less reliable compared to the A1248 hatchability TRV because the survival TRV is based on sparser data requiring interpolation over a much wider dose gradient.

A1242 exhibits two dose-response patterns in chicken studies--one with TRVs somewhat lower than A1248, and another approaching the A1254 TRVs. The two A1242 patterns may be due to differences in A1242 batches, chickens, feed, or experimental designs. Instead of choosing between the two patterns, both sets of A1242 TRVs are shown.

TRVs calculated from exposure to commercial PCB products may underestimate the toxicity of PCBs in the field because of environmental weathering and selective retention in biota that alter the proportions of dioxin-like congeners compared to the source product. Concurrent exposures to other chemicals in the field that contribute to dioxin-like toxicity reduces the margin of exposure to PCBs that can be tolerated without exhibiting adverse effects. Use of the lower of the TRVs given above is recommended to account for increased toxicity due to these effects (A1254 TRVs for mink and A1248 TRVs for birds). The TRVs are probably not applicable to sites

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[1] The literal meaning of *in vitro* is "in glass", which refers to experiments performed outside of a living body, for example, in test tubes , petri dishes., or other laboratory apparatus. In this case, the bioassay measures the response of cultured cells to PCBs and other chemicals with dioxin-like toxicity.

with source PCBs different from the Aroclors assessed in this effort, for example, A1260, which is less toxic than A1242, A1248, or A1254 in an *in vitro* mammalian bioassay (Tillitt, et al. 1992).

The methodology used for deriving the TRVs was internally peer-reviewed by USEPA scientists. The peer review charge included review of the data normalization procedure for combining the results of different studies, effect size selection, linear interpolation method (including the following modifications–restriction of interpolation to the linear portion of the data plots, use of log-linear interpolation, no adjustment for violations of monotonicity for hormetic responses, and lack of confidence interval estimation), and adjustment of mink TRVs for increased toxicity associated with continuous exposure over 2 breeding seasons or 2 generations. The peer reviewers also made additional comments regarding meta-analysis, uncertainty associated with Aroclor approaches, TEQ as an alternative approach, and editorial comments. The peer review comments and responses are summarized in Responses to Peer Review Comments, Wildlife PCB Toxicity Reference Values. March 6, 2003. USEPA Region 5 Superfund Division, Chicago. The present version of this work product has been revised in accordance with these comments and responses.

2 Acronyms

A1242, A1248, A1254, A1260 - different Aroclors (commercial PCB products produced in America)
A50 - one of the Clophen commercial PCB products produced in Europe
AhR - aryl hydrocarbon receptor (cellular protein that binds with dioxin-like chemicals in the initial step of a cascade of interactions leading to expression of toxic effects)
AWQC - federal ambient water quality criteria
BMF - biomagnification factor (= concentration in animal / concentration in food or environmental media)
BW - bodyweight
Ca^{2+} - calcium ion
d - day
EC_x - effective concentration resulting in a treatment response x % less than the control response
ED_x - effective dose resulting in a treatment response x % less than the control response
fw - fresh weight (weight including moisture content at the time of measuring)
g - gram
GLI - Great Lakes Initiative
H4IIE - designates a particular cultured rat cell line used in an *in vitro* bioassay for dioxin-like activity
I-TEF - international toxic equivalency factors
kg - kilogram (1000 g)
LD_{50} - lethal dose to 50 % of the exposed population
LOAEL - lowest observed adverse effect level (lowest tested dose that caused a statistically discernible response compared to the control group)
LOEC - lowest observed effect concentration (lowest tested concentration that caused a statistically discernible response compared to the control group)
lw - lipid weight (concentration on a lipid (fat) basis, e.g., mg PCB per kg fat)
mg - milligram (0.001 g)
pg - picogram (one trillionth gram)

NOAEL - no observed adverse effect level (highest tested dose that did not cause a statistically discernible response compared to the control group)
NOEC - no observed effect concentration (highest tested concentration that did not cause a statistically discernible response compared to the control group)
OECD - Organization for Economic Co-operation and Development (Europe)
PCB - polychlorinated biphenyl
ppb - parts per billion (equal to 0.001 ppm)
ppm - parts per million (equal to mg/kg)
ppt - parts per trillion (equal to 0.000001 ppm or pg/g)
PRG - preliminary remedial goal
REP - relative potency (the fractional response of a dioxin-like chemical compared to 2,3,7,8-TCDD in a particular test or approach)
RR - relative response (normalized treatment response = treatment response / control response of the same study)
TCDD - tetrachlorodibenzo-*p*-dioxin
TEF - toxic equivalency factor (the consensus fractional response of a dioxin-like chemical compared to 2,3,7,8-TCDD based on variety of research approaches and results)
TEQ - toxic equivalent concentration (the concentration of 2,3,7,8-TCDD that is expected to equal the potency of a mixture of dioxin-like chemicals, calculated by multiplying the concentrations of each dioxin-like chemical by their respective TEFs, or measured directly by an *in vitro* bioassay)
TRV - toxicity reference value (the concentration or dose of a chemical used to assess risk–no effect TRVs are not expected to cause adverse effects, and low effect TRVs are the levels at which adverse effects first become apparent)
USEPA - United States Environmental Protection Agency
WHO - World Health Organization
wk - week
ww - wet weight (weight including the normal moisture content)

3 Background

One of the issues raised concerning the Baseline Ecological Risk Assessment for the Allied Paper, Inc./Portage Creek/Kalamazoo River Superfund site concerns the appropriate PCB TRVs for wildlife. Inclusion of studies performed with field-contaminated prey from Saginaw Bay, MI, in the derivation of PCB TRVs for mink and birds was criticized because the observed effects may have been confounded by contaminants other than PCBs.[2] One of the alternatives suggested in written and oral comments was to use the TRVs developed for the Great Lakes Initiative (GLI) water quality criteria (WQC) for wildlife (USEPA 1995a). This was looked into, but a difficulty occurred in attempting to apply the TRVs used by the GLI to Superfund purposes.

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[2] Whether PCBs appear to be major or minor contributors to the observed toxicity in the Saginaw Bay studies depends on which set of toxic equivalency factors (TEFs) are used to convert the measured contaminant data to dioxin toxic equivalents (TEQs). PCBs are the major contributor according to the International TEF (I-TEF) scheme, but are minor contributors according to the TEFs [better termed relative potencies (REPs) because they are based on a single experimental approach] reported for the H4IIE bioassay (an *in vitro* assay performed with a rat hepatoma cell line) (Tillitt, et al. 1996; Geisey, et al. 1997). The I-TEF scheme has been replaced by World Health Organization TEFs (WHO-TEFs) (Van den Berg, et al. 1998), but the new scheme does not significantly alter the outcome.

The GLI WQC are based solely on the no observed adverse effect level (NOAEL), but the guidance for Superfund ecological risk assessments recommends evaluation of risks and calculation of site-specific preliminary remedial goals (PRGs) for both the NOAEL and lowest observed adverse effect level (LOAEL) (USEPA 1997). At first this did not appear to be problematic since the GLI reported both the available NOAELs and LOAELs of the studies reviewed for calculating the WQC. The issue in applying these TRVs for Superfund use is that the GLI did not evaluate the appropriateness of the LOAEL data for regulating LOAEL-based risks. The mink assessment represents an extreme example. The LOAEL chosen by the GLI for mink reproduction resulted in complete kit mortality--only 2 of 7 exposed females whelped (gave birth), producing only 1 live but underweight kit that died before reaching 4 weeks age (Aulerich and Ringer 1977). Since a NOAEL was not identified in this study, the LOAEL was converted to a NOAEL by dividing by an uncertainty factor of 10 (USEPA1995a). The calculated NOAEL was equivalent to the NOAEL of a mink feeding study performed with field-contaminated fish, which indicated that the conversion provided an adequate margin of safety for ensuring no adverse effects (USEPA 1995a), and therefore satisfied the objectives of the GLI WQC. However, at the LOAEL, zero successful reproduction is not an adequate representation of a lowest adverse effect level, instead it represents the maximum possible adverse effect on reproduction, and therefore does not satisfy the Superfund objectives of characterizing the risk range between no effects and the level at which adverse effects become detectable.

The problem in applying the LOAEL identified by the GLI is inherent in the methodology of the NOAEL/LOAEL approach, which has been criticized in numerous publications (for examples see Crump 1984; Suter 1996; OECD 1998; Crane and Newman 2000). The main limitations of the NOAEL/LOAEL approach are that the values are significantly affected by factors other than toxicity, and the available dose-response information is not utilized. NOAELs and LOAELs are statistically defined–a LOAEL is the lowest tested dose that exhibited a statistically discernible response compared to the control response, and a NOAEL is the highest tested dose that did not show a statistically discernible response from that of the control. An obvious issue is that, by this approach, NOAELs and LOAELs are restricted to the particular doses tested. This is the source of the problem with the GLI selected LOAEL for mink–the lowest treatment dose tested resulted in 0 % successful reproduction, so by default, it was identified as the "lowest" adverse effect level, even though it is obvious that lower doses, if tested, would also show adverse reproductive effects. Also, determination of statistical significance depends not only on toxicity, but also on the study design (the particular dose levels tested and number of replicates per dose) and the particular statistical procedure chosen to compare the treatment and control responses, all of which affects the statistical power of the comparison. An unfortunate result is that "poor" studies with low statistical power are rewarded from the perspective of potentially liable parties because they result in higher (less protective) NOAELs and LOAELs compared with more rigorous and expensive studies with higher statistical power. Similar considerations pertain to the number of dose levels tested–fewer doses are less expensive, but may "miss" appropriate effect levels by wide margins. Another way of considering these issues is that, because of the widely ranging statistical power associated with toxicity tests, and differences in the doses selected for study, the level of adversity associated with statistically determined TRVs varies uncontrollably. For example, in a ring test of aquatic toxicity laboratories, the mean decrease in response associated with the statistically identified no observed effect concentration (NOEC) was about 10 % across laboratories, but ranged as high as 37 % in individual cases (cited in Crane and Newman 2000). In another evaluation, statistically determined no effect concentrations could be associated with as much as 50 % decreases in responses compared to controls depending on the data and the choice of statistical method, leading

the investigators to conclude that "the NOEC is rarely if ever an indicator of no effect" (Crane and Newman 2000). The same issues apply to LOAEL determinations. Another limitation of the NOAEL/LOAEL approach is that it does not make use of the available dose-response information. See Crump (1984) for an example showing how statistically determined effect levels can give misleading results for chemicals with markedly different dose-response patterns.

An alternative is to use the data from toxicological studies to develop dose-response relationships, and to use the relationships to determine the no-effect and low-effect doses that correspond to selected effect levels. This frees the analysis from the specific doses used in a study (a TRV can now be interpolated between the tested doses), and from the non-conservative bias of tests with inadequate statistical power. In this approach, the effect size is selected first (effect size is the percentage decrease in performance compared to control), for example, that the low effect level should be a 20 % decrease in treatment response compared to the control response. Then the dose corresponding to the selected effect size is determined from the dose-response relationship. This approach is referred to as "ED_x" or "EC_x", where ED is effective dose, EC is the effective concentration, defined as the dose or "concentration that produces a specified size of effect relative to an untreated control" [3] (Chapman 1998), and x represents the effect size--the selected change in response compared to the control response (for example, the dose resulting in a decrement in response of 25 % is designated as ED_{25}). A particular ED_x (the dose that would result in a decrease in performance by the percentage chosen as the effect size) may be determined from dose-response data through several procedures including graphical techniques, calculation from a fitted equation, or interpolation between the measured responses that bracket the selected effect size. A modification is to calculate the TRV for the lower confidence limit of the data, which is termed a "benchmark dose" (USEPA 1995b).

Some of the advantages of the ED_x approach for determining TRVs are that the size of the effect is known (because it is selected beforehand), the TRVs are not constrained to the particular doses tested (because they are determined from the dose-response relationship revealed by the test data), the TRVs do not depend on the particular statistical test chosen, and confidence intervals can be calculated. One of the main limitations is in choosing the appropriate regression model for curve-fitting approaches. Confidence limits may be quite large for threshold [4] and hormesis [5] models (Chapman 1998). Also, determination of TRVs for very low effect levels (less than ED_{10}) becomes strongly model dependent (Moore and Caux 1997; Scholze, et al. 2001). Fortunately, determination of TRVs for effect levels greater than 10 % has low model dependence, that is, the choice of

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[3] Dose is the rate of exposure of an animal or plant to a chemical, usually expressed as the amount of chemical per unit bodyweight per day. Instead of dose, the concentration of the chemical under investigation may be given for contaminated media (water, soil, air), food, or in a tissue or the whole body of the exposed animal or plant.

[4] For threshold models, treatment responses are flat (not different from the control response) at low doses until a critical level of dose is reached above which the treatment responses decrease as the dose increases.

[5] Hormesis refers to enhanced responses (treatment responses greater than control responses) at low doses of a chemical that has adverse effects at higher doses. For hormesis, treatment responses are flat (same as control) as the dose initially increases above the control dose, but, before reaching the critical threshold for adverse effects, the treatment responses become greater than the control response. As the critical threshold is approached, the treatment response decreases to the control level, and, as the doses increase above the critical threshold, the treatment responses decrease below the control response (adverse effects occur).

regression model has relatively minor effects on TRVs when calculated for ED_{10} or higher (Moore and Caux 1997).

An ED_x approach therefore is applied to the PCB toxicity data for mink and chicken to develop TRVs appropriate for assessing the risk range between no effect and low effect levels.

Although congener-specific analyses are recommended for assessing risks to PCBs, Aroclor-based toxicity reference values (TRVs) are still useful for several reasons. 1) The PCB database at many sites is predominantly or solely Aroclor data. This is especially true of historic data. 2) At contentious sites, the lengthy process for resolving disagreements has resulted in a need to finalize Aroclor-based risk assessments initiated prior to the current emphasis on congener-based approaches. In these situations, abandonment of the an Aroclor approach could entail substantial delay and cost for resampling media and biota to provide synoptic congener data. 3) There is a large database available on the ecotoxicological effects of PCBs on an Aroclor basis. 4) The utility of the available TEQ-based ecotoxicological studies is compromised by the use of inconsistent toxic equivalency factors (TEF). Conversion to a common TEQ basis is feasible only if the original congener data is reported so that the TEF scheme of choice can be applied (Dyke and Stratford 2002), but the underlying congener data are rarely reported in journal articles, which reduces the pool of comparable TEQ studies. Results of *in vitro* bioassay TEQs cannot be directly compared to calculated TEQs because bioassay results and congener relative potencies (REPs) may vary with changes in test protocols, for example, the solvent for dosing the cells (Tillitt, et al. 1991), exposure time (Clemons, et al. 1997), or the species from which the cell line is derived (Aarts, et al. 1995); and bioassays may show responses to chemicals not having significant effects in animals because of toxicokinetic processes not present *in vitro*. 5) The currently available TEQ approach assesses only toxicity related to aryl hydrocarbon receptor (AhR)-mediated processes (dioxin-like effects). Although AhR-mediated effects are frequently reported to be more sensitive endpoints compared to non-AhR effects, it is not clear how generally this relationship applies across taxa and endpoints. In the absence of a non-AhR TEF scheme, an Aroclor-based assessment can provide an indication whether significant non-AhR effects may have been missed in a TEQ-based assessment.

4 Methods

4.1 Linear Interpolation

The effluent toxicity testing guidance in the water program (e.g., Klemm, et al. 1994; Chapman, et al. 1995) is modified for deriving PCB TRVs from multiple mink or chicken studies. The guidance recommends linear interpolation between the treatments showing effects that bracket the chosen effect level. The linear interpolation method avoids the complications associated with selection of the appropriate regression model by focusing on the mean dose-response trend in the region surrounding the chosen effect level. Confidence intervals are then calculated through a bootstrap method. The method assumes monotonicity, that is, that the mean response decreases as the test concentration increases, and data are smoothed (adjusted) if this pattern is violated.

The linear interpolation method was developed for deriving TRVs from the results of individual toxicity studies. However, for the present effort, the results of multiple studies are combined to better reveal the shape of the

dose-response relationship for PCBs. This is necessary because most of the individual PCB toxicity studies tested a limited number of doses. Interpolation is strictly implemented for this effort–no extrapolations beyond the empirical data range are performed.

The first modification is to normalize the data so multiple studies can be compared on a common basis. The reason for combining research results is to better define the shape of the dose-response relationship compared to that shown by the relatively low number of doses tested in any single experiment (Section 4.7). Normalization is accomplished by dividing each mean treatment response by the respective mean control response (Equation 1). Two examples of this normalization procedure for combining multiple studies are Leonards, et al. (1995) and Tananka and Nakanishi (2001) (the latter normalized both response and exposure concentration, but only response is normalized for the present effort). The normalized responses are termed "relative response" (RR).

RR = treatment response / control response of the same study [1]

The relative responses are plotted on semi-log graphs (base 10 logarithm dose or concentration vs. relative response). The plots showing interpretable dose-response relationships (Section 6.1.1) are used to derive the no- and low-effect TRVs by a linear interpolation between the treatments that bracket the effect level of concern. The plots showing obviously inconsistent dose-response relationships, either because there is no relationship or because the combined studies are incompatible for some reason, are excluded for TRV derivation.

The second modification is interpolation is only performed when the selected effect size falls within the steep linear portion of the dose-response plot. There are two purposes: 1) the linear interpolation method is applicable to linear responses, but will over- or underestimate for nonlinear portions of the dose-response relationship; and 2) this avoids interpolation over excessively large exposure gradients for which the shape of the dose-response relationship is poorly known. The practical result is that most of the interpolations are performed between relatively small gradients in exposure values. The majority of the TRV interpolations for mink occur between treatments that differ in dietary concentrations by 2-fold or less, with the largest difference for the interpolations for Clophen A50 and live kits (3-fold for exposure over 2 breeding seasons, and 5-fold over 1 breeding season). Interpolation is not performed for the TRV for A1254 and kit survival, for example, because there is a 100-fold difference between the dietary concentrations of the treatments that bracket the target low-effect response. Many of the bird TRVs are interpolated between small gradients (2- or 3-fold for A1242 or A1248 dose and hatchability, less than 4-fold for A1254 dose and hatchability, and 2-fold or less for A1242 or A1254 egg residue and hatchability). A few bird TRVs are interpolated over larger gradients (6- fold for A1242 egg residue and chick bodyweight, 7-fold for A1248 egg residue and hatchability, and 10-fold for A1242 or A1248 dose and chick bodyweight, and A1248 dose and survival). Interpolations are not performed for greater than 10-fold differences in treatment doses.

A third modification is log-linear interpolation (Equation 2) is used since it gives a better fit within the linear portion of the data plots compared to the linear interpolation in the guidance.

$$\mathrm{Log}_{10}\,TRV = \mathrm{Log}_{10}\,C_j + (((M_1 * P) - M_j) * ((\mathrm{Log}_{10}\,C_{j+1} - \mathrm{Log}_{10}\,C_j) / (M_{j+1} - M_j))) \quad [2]$$

$$TRV = 10^{\,\mathrm{Log10\,TRV}}$$

Where TRV is the interpolated toxicity reference value, P is the chosen effect size (Section 4.2), M_1 is the control relative response (1.0 by definition because the response data is normalized to controls), C_j is the test concentration of the treatment that produced a relative response (M_j) greater than P, and C_{j+1} is the test concentration of the treatment that produced a relative response (M_{j+1}) less than P. The symbols used in Equation 2 are the same as the ones in the guidance for effluent toxicity testing. Equation 2 is used for interpolating TRVs on the basis of PCB concentration in mink diet or chicken eggs. A similar equation is used for interpolating TRVs on the basis of bodyweight-normalized dose to chicken, where C is replaced by D for dose.

A fourth modification is data are not smoothed when treatment responses exceed control responses (relative responses > 1) to allow for hormesis (enhanced response at very low doses). One of the response patterns used for bird TRV derivation, chick bodyweight vs. A1242 egg residues (Figure 27), was attributed to hormesis by the investigators (Gould, et al. 97). The same investigators also reported a hormetic effect of A1254 on chick bodyweight (Figure 26). Gould, et al.'s conclusion is accepted because hormesis is evident at two dose levels for two different endpoints. All three of the commercial PCB products tested in mink feeding studies show possible hormetic effects on the number of live kits per mated female (Aroclors 1242 and 1254, and Clophen A50) (Figures 2, 3, 7). Hormesis is evident in the Clophen A50 experiment for exposure durations of both 1 and 2 breeding seasons (Figure 7). This effect is also shown by some of the feeding trials performed with field-contaminated prey for the same endpoint (Figures 8 and 13). Therefore, acceptance of hormetic responses is justified for the effects of egg residues on chick bodyweight (as attributed by the researchers), and the effect of dietary exposure on the number of live kits per mated female mink (exhibited in multiple studies). This indicates that adjustment of deviations in monotonicity is unwarranted for a treatment response exceeding the control response. The same modification to the linear interpolation method to allow for potential hormesis was made in a recent comparison of techniques for calculating effective doses (Isnard, et al. 2001). Data smoothing for monotonicity is performed in a few cases when the treatment responses are less than the control response, that is, when hormesis can not explain the deviations (documented in the notes to Tables 2 and 3).

A fifth modification is the procedure for deriving confidence intervals is not implemented since the only available data from the published mink and chicken studies are the treatment means (the underlying data for the individual replicates were not presented for any of the studies). The bootstrapping method for generating confidence intervals for the linear interpolation method requires the full replicate data.

An additional modification was made for the mink TRVs only. Two mink feeding studies, one performed with Clophen A50-supplemented feed and one with field-contaminated prey, reported the reproductive effects of PCBs associated with exposures over both one and two breeding seasons, and the latter study also reported the reproductive effects in two generations of exposed females. Both studies showed increased adverse effects in the second year or generation of continuous exposure. Since only single-season exposures have been reported for commercial Aroclor feeding studies, TRVs protective for long-term occupancy of a site by female mink are calculated by multiplying the single-season Aroclor TRVs by the mean ratio of the Clophen A50 and field-contamination TRVs for exposure over two breeding seasons or generations divided by the corresponding TRVs for single-season exposure in the same studies (the ratios are given in Table 2).

4.2 Effect Size

Effect size is the amount of decrease in response of animals or plants exposed to a chemical compared to unexposed controls that is selected as the level of concern for assessing risk (the x of ED_x, Section 3). The selected effect sizes for this effort are not based on receptor-specific life history/population models. The bird TRVs, derived from chicken data, are intended to provide conservative TRVs for application to species of unknown sensitivity to PCBs, for which no single population model would be applicable. The mink TRVs may also be applied to mammalian receptors of unknown sensitivity to PCBs (this requires bodyweight normalization of the mink dietary TRVs), in addition to mink for which it is derived. The effect sizes used in this effort are chosen for pragmatic reasons–to minimize model dependence, approximate the power of well-designed toxicity studies, and maintain general consistency in approach with other regulatory uses of toxicity test data. In short, to select a low effect size that is expected to be detectable in a well-designed study, and is reasonably consistent with prior Agency practice. The very steep PCB dose-response plots make the question of the appropriate low effect level somewhat moot, since there is a small range between no-effect and total-effects levels.

A pragmatic consideration is to avoid choosing an effect size for which interpolation may be strongly model dependent. In an examination of aquatic toxicity data sets, Moore and Caux (1997) concluded that interpolation becomes strongly model-dependent for less than 10 % decreases in response compared to that of controls (see also Scholze, et al. 2001). The various models gave reasonably consistent results for response differences of at least 10 % compared to controls. A related consideration is the effect size commonly associated with statistically-determined lowest observed effect concentrations (LOECs) in well-designed toxicity studies. The LOECs of the toxicity studies for the ambient water quality criteria (AWQC) and pesticide programs generally correspond to 20 to 25 % effect sizes (Suter, et al. 2000), and interpolation of the 25 % effect size is recommended for effluent toxicity testing (e.g., Klemm, et al. 1994; Chapman, et al. 1995). Another pragmatic consideration is consistency with the basis for regulatory decision-making in other programs that utilize toxicity testing results. A *de minimis* effect size of 20 % was identified in one such review (summarized in Suter, et al. 2000) [note: this is not a standard written in the regulations, but the minimum effect size associated with regulatory actions in practice].

This indicates that a reasonably detectable effect size consistent with Agency practices in other programs would fall between 20 and 25 %. The higher of these values is chosen for this effort to ensure that the low effect size represents a non-trivial departure from the control response (equivalent to 75 % relative response). In other words, the interpolated low effect TRV is the ED_{25} or EC_{25}.

The no effect size is set a t 10 % (relative response of 90 %), so the interpolated no effect TRV is the ED_{10} or EC_{10}. Similar to the rationale for the choice of low effect size, 10 % is chosen for no effect size because it is unlikely to be identified as a LOAEL in a reasonably well-designed toxicity study, is lower than the *de minimis* effect-level identified in a review of regulatory decision-making, but is at the minimum size so that the calculated ED_{10} is not strongly model-dependent (various regression techniques will likely give similar values).

The effect sizes could be further refined by linking them to species-specific population models to derive effect levels from projected population dynamics–the models probably need to be both region- and habitat-specific, but even so, there may be significant uncertainty (Section 6.1.6). However, because of the nature of the dose-response relationships for PCBs and reproductive endpoints in mammals and birds, such refinement would have relatively minor impact on the final TRV values.

The question of the appropriate value for the low effect size is made somewhat moot by the very steep dose-response plots for PCBs. For example, the A1248 oral dose to hens associated with complete hatch failure (~1 mg/kg-d) is less than 3 times greater than the dose showing no effect (~0.4 mg/kg-d) (Figure 19). The same is true for mink endpoints. Live kit production is completely suppressed at a dietary concentration of 5 mg/kg A1242, but no effect is reported at 2 mg/kg (exposure over a single breeding season) (Figure 2). The range in A1254 dietary concentrations for the same endpoints are 2 and approximately 1 mg/kg, respectively (exposure over a single breeding season) (Figure 3). Refinements of the effect level will therefore produce only relatively small changes in the TRVs.

4.3 Study Selection

Study results are selected according to the following criteria: 1) studies published in journals (gray literature [6] excluded), 2) primary sources (secondary sources [7] excluded), 3) matched control and treatment responses, 4) continuous PCB exposure up to or through the initiation of breeding (responses following cessation of exposure are excluded if sufficient time elapsed to allow depuration [8] to occur prior to breeding), and 5) treatment responses individually reported by dose and Aroclor (aggregated responses based on combinations of exposure levels or combinations of Aroclors are excluded). The individual Aroclor constraint is not applied to studies with field-contaminated prey. Statistical significance is not a criterion for selection of treatments within a study since the objective is to develop dose-response relationships over the full gradient tested (treatments that do not differ from the control response are as important for delineating the dose-response relationship as the treatments that do differ). When response data are reported for more than one exposure time, data for later exposure periods take precedence over earlier exposure periods or data averaged over the entire exposure period. Data are taken from text, tables, or figures so long as the selection criteria are met.

Only studies in which the test animals were exposed to commercial PCB products are used for calculating TRVs. Studies performed with field-contaminated prey are not directly used for calculating TRVs (to avoid possible confounding effects of contaminants not occurring in PCB products), but are included to contribute to the weight-of-evidence for response trends (e.g., evidence of hormesis), to contribute to the estimation of the proportional change in mink responses when the exposure duration increases from one breeding season to two breeding seasons or generations, and for overall comparison with Aroclor studies. Aroclor and field contamination studies are plotted separately for mink, but since only one chicken study is included with field-contaminated feed, it is plotted on the same graphs with chicken Aroclor studies to conserve space (the field-contaminated study is shown as "PCB" in Figures 17, 21, 25, 26, and 29-31).

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[6] Gray literature refers to studies not published in journals or books, or abstracts of results that provide insufficient information on methods and data. Examples of gray literature include meeting abstracts , govemment reports, master's or doctoral theses, unpublished research notes, and prepublication drafts.

[7] Primary sources are to the original publications reporting research results. Secondary sources are review articles, compilations, or other summaries of previously published work.

[8] Depuration is the elimination of chemicals from an animal after the cessation of exposure, through metabolic conversion and/or excretion.

Of the studies used for TRV derivation, only one did not continue exposure throughout breeding. Käkelä, et al. (2002) exposed mink to A1242-supplemented food for 21 weeks, but then switched to the control diet at the onset of breeding. This treatment is included because there was no delay between the cessation of A1242 exposure and initiation of breeding, therefore depuration did not occur prior to breeding. The sole TRV calculation involving this treatment is for live kits per mated female for A1242, in which the Käkelä, et al. datum is consistent with the trend of the other studies (Figure 2).

One of the "field-exposed diet" studies (mink fed meat from A1254-exposed cows) reported the control response for only one of the endpoints in the study (live kits per mated female) (Platanow and Karstad 1973). Other responses are included only when the treatment response was zero (e.g., 0 % kit survival in the 0.64 ppm treatment), because the relative response in this case is not affected by the specific value of the control response. This study is not included in the A1254 TRV derivation because A1254 was not fed directly to mink. The bioaccumulation process in cows increased the toxicity of the PCBs to the next higher trophic level (animals feeding on cows) as does bioaccumulation in wild animals (PCB toxicity to predators is usually greater than to their prey), so this study is included as one of the field-exposure studies.

It is not feasible to exactly match the exposure durations between studies. Exposure durations range from 6 to 14 wk for chicken feeding studies, with most between 6 and 9 wk (Table 7) (an individual 39-wk treatment by Platanow and Reinhart (1973) is not used for TRV derivation), and from 3 to 10 months for mink studies performed over a single breeding season (Table 6) (the results of the 2-month exposure duration by Jensen (1977) is not used for TRV derivation because the type of PCB in this study was not identified). For mink, the studies are segregated by the number of breeding seasons exposure was maintained (the results of exposure over 2 breeding seasons or 2 generations are analyzed separately from 1-season results). The data show no obvious effects due to the range in exposure durations (other than the 1-season vs. 2-season or 2-generation results for mink which are therefore disaggregated) (see Sections 6.1.2 and 6.1.5 for further discussion).

The exposure route for all of the mink studies is the same–contaminated diet. For oral dose to chicken, the exposure route is contaminated diet with one exception–contaminated water in the study by Tumasonis, et al. (1973). The data do not show an effect related to this difference in exposure media. The relative effect due to exposure to contaminated water is consistent with the effect trends of exposure to contaminated diet (Figures 20 and 24). As it turns out, the Tumasonis, et al. results had no direct influence any of the TRV interpolations. For egg concentration, the exposure route was through maternal dietary exposure except for Gould, et al. (1997) in which PCBs were injected into egg yolks on day 0 of incubation. The Gould, et al. study influenced one TRV (chick bodyweight vs. A1242 egg residue). Again, the response trend is consistent between exposure routes (Figure 27) (see Section 6.1.3 for further discussion).

4.4 Toxicity Endpoints

Data for the following reproductive and growth endpoints were collected from a review of mink PCB studies: whelping frequency (number of female mink giving birth / number mated), total kits (live and stillborn at birth) per whelped female, live kits per whelped female (at birth), live kits per mated female (at birth), kit bodyweight, and kit survival (Table 4). Since the effects of the first three endpoints are integrated in the number of live kits per mated female, TRVs are not separately calculated for whelping frequency or for total or live kits per whelped

female. Kit bodyweight and survival are reported for various times following birth as given in the original studies. TRVs are calculated for kit bodyweight at birth, but not for later times, because the database for later times is smaller than for bodyweight at birth. Kit survival was reported for 4 to 6 weeks following birth in the studies used for TRV derivation.

For chicken PCB studies, the toxicity endpoints include egg productivity, egg fertility, hatchability, chick bodyweight, chick survival, and chick deformity. To maintain comparability among the dose-response plots (reduced response at higher doses for endpoints exhibiting a relationship with PCB exposure), chick deformity is converted to chick normality, that is, the relative proportion of chicks *without* deformities is plotted. Chick normality is calculated as 1.0 - the proportion of deformed chicks. As with other endpoints, treatment normality is divided by the corresponding control normality to calculate the relative response, in this case, relative normality (or normalized normality!).

4.5 Data Conversions

Normalization of response data is discussed in Section 4.1. The data sources, relative response calculations, and other data conversions are documented in Tables 6 and 7.

The mink dietary PCB concentrations are as given in the original studies when available. Two studies expressed the exposure in terms of daily ingestion (mg PCB/mink/d), instead of dietary concentration (Brunström, et al. 2001; Kihiström, et al. 1992). The dietary concentration is calculated by dividing the daily PCB ingestion by the daily food ingestion reported in each study (see notes to Table 6). For some of the study results, the reported data are converted to make them consistent with the toxicity endpoints assessed in this effort. For example, if the number of live kits per mated female is not given in the original study, it is calculated by multiplying the number of live kits per whelped female by the fraction of females whelped of those mated. The conversions are documented in the notes to Table 6.

The chicken dietary PCB concentrations are converted to bodyweight-normalized doses by multiplying by the food ingestion rate reported in the study, or by a default leghorn hen food ingestion rate of 0.067 kg feed/kg_{BW}-d (Medway and Kare 1959). For the single study with PCB exposure through water (Tumasonis, et al. 1973), the bodyweight-normalized dose is calculated by multiplying the PCB concentration in water by the reported daily water consumption per hen divided by the reported hen bodyweight (see note to Table 7). When egg PCB concentrations were reported for egg yolks, the data are converted to whole-egg concentrations by multiplying by 0.364, the proportion of yolk in chicken eggs on a wet weight basis (Sotherland and Rahn 1987).

The relative "chick" normality (see Section 4.4) for Lillie, et al. (1975) is based on abnormal embryos, not on deformities in hatched chicks. However, data are insufficient for deriving deformity-based Aroclor TRVs. The relative "chick" bodyweight for Gould, et al. (1997) is based on 17-d embryos, not on hatched chicks. This data set plays an important role in the A1242 egg TRVs for chick bodyweight.

4.6 Presentation

The source data, data conversions, and relative response calculations are documented in Tables 6 and 7. The relative responses are summarized in Tables 4 and 5, and plotted in Figures 1-32 in semi-log graphs (dose or concentration on a base 10 logarithmic scale). To aid interpretation, the data points of commercial PCB feeding studies that exhibit interpretable dose-response relationships are linearly connected in the figures showing the effects of a single commercial product (an exception is made for Figures 25 and 28 because of the small number of data points). Data points are also linearly connected in the figures illustrating the Restum, et al. (1998) study performed with field-contaminated diets because the results are used in part to estimate the effect of increasing exposure duration from 1 breeding season to 2 breeding seasons or generations. Data are presented as scatterplots (unconnected) in the figures simultaneously showing the effects of multiple Aroclors or multiple field-contaminated diet studies on an individual toxicity endpoint, and in the figures of endpoints that do not exhibit an interpretable dose-response relationship.

The TRV interpolations are presented in Tables 2 and 3. Although the TRVs are derived through calculation, and not through a graphical approach, their derivation can be visually understood by examining the figures. The low effect size is shown in the figures for endpoints used for TRV derivation by a horizontal line indicating 0.75 relative response (effect size of 25 %). The low effect TRV (ED_{25} or EC_{25}) is represented by the dose or concentration corresponding to the intersection of the 0.75 relative response line and the line connecting the scatterplot data. The two data points nearest to the intersection are the data used for interpolation (see Tables 2 and 3 for the sources and values of the interpolation data). Similarly, a no effect TRV (ED_{10}) is the intersection of the 0.90 relative response line (not shown) and the line connecting the scatterplot data.

4.7 Example

A comparison between the results of individual studies and combined studies is illustrated in Figure 16 for the effect of A1248 dose to hen on hatchability. The 9 mean data points in this plot come from 3 studies–one contributing 4 means, one 3 means, and another 2 means (the exposure durations of these 3 studies are similar, 8 to 9 wk). There is an internally consistent dose-response relationship based on the combined data that exhibits a threshold for significant adverse effects above 0.3 mg/kg_{BW}-d, with a steep decrease in hatchability to nearly complete suppression above 1.0 mg/kg_{BW}-d. Based on the combined data, the interpolated no effect TRV (ED_{10}) is 0.38 mg/kg_{BW}-d, and the low effect TRV (ED_{25}) 0.48 mg/kg_{BW}-d (Table 3). Taken individually, the interpolated ED_{25} for the separate studies are approximately 0.2, 0.25, and 0.45 mg/kg-d. Two of the studies provide inaccurate estimates of the ED_{25} because the doses chosen for those studies do not adequately reveal the steep portion of the dose-response relationship. In both cases, the doses used for interpolation differ by an order of magnitude, that is, interpolation is performed over a 10-fold dose gradient The one study (Lillie, et al. 1975) that adequately reveals the steep portion of the dose-response relationship was performed with closely spaced doses (2-fold gradients) specifically selected between the doses showing no and severe effects in an earlier investigation by the same research group.

Statistical analyses were presented in two studies [9] for the effect of A1248 dose on hatchability. The NOAEL was 0.12 mg/kg_{BW}-d (2 ppm treatment), and LOAEL 1.2 mg/kg_{BW}-d (20 ppm treatment) for Lillie, et al. (1974). Compared to the dose-response relationship in Figure 16, the NOAEL is much lower and LOAEL much higher than the actual threshold for effects. In the study by Scott (1997), the NOAEL was 0.07 mg/kg_{BW}-d (1.0 ppm treatment) and LOAEL 0.67 mg/kg_{BW}-d (10 ppm treatment). In this case, the LOAEL is closer to the ED_{25} of the combined data, but the NOAEL is much lower than the ED_{10}, in other words, one treatment dose was fortuitously chosen that fell within the narrow transition between no and severe effects, but the 10-fold gradient to the next lower dose tested was too large to adequately represent the threshold for adverse effects.

5 Results

5.1 Mink Studies

The results of mink studies are shown in Figures 1-15. Exposure-response relationships are evident for number of live kits per mated female (Figures 1-3, 7, 8, and 13), kit bodyweight (Figures 5, 9, 10, and 14), and kit survival (Figures 11, 12, and 15). Data were also normalized for whelping frequency, total kits per whelped female, and live kits per whelped female, but these effects are integrated in the live kits per mated female endpoint, so are not separately analyzed.

The interpolated TRVs are given in Table 2. The dietary TRVs (mg/kg ww) for exposure in a single breeding season are as follows: A1242–2.5 (no effect) to 2.7 (low effect) for live kits per mated female; A1254–1.0 (no effect) to1.1 (low effect) for live kits per mated female and 1.1 (low effect) for kit bodyweight; and Clophen A50–2.4 (no effect) to 3.1 (low effect) for live kits per mated female. The A1254 TRVs for kit survival cannot be interpolated because of data complications (described below) and, for the no effect TRV, excessively large dose gradients, but are greater than 0.02 and less than 1.0 mg/kg ww diet.

The A1254 relative response for kit survival appears to show a no effect level of 1.0 mg/kg ww (Wren, et al. 1987) and complete mortality at 2.0 mg/kg ww (Aulerich and Ringer 1977) (Figure 6). Although Wren, et al. (1987) show the same kit survival for controls and the 1 mg/kg treatment, they reported a dramatic shift in the cause of the mortality in the two groups–mainly trauma and infection in the control kits (9 of 12 kits that died after birth), but predominantly starvation in the treatment kits (13 of 14 treatment kits that died after birth). In contrast, they reported that none of the control kit mortality was due to starvation. These observations raise the possibility that the treatment mortality might have been related to wasting syndrome, a "starvation-like" syndrome of chemicals with dioxin-like effects (Seefeld, et al. 1984; Lu, et al. 1986). Although the Wren, et al. study does not prove that wasting syndrome occurred, the major shift in the causes of mortality between the treatment and control groups indicates that there is substantial uncertainty in concluding that the 1 mg/kg treatment is, in fact, the no effect dietary concentration for kit survival in the Wren, et al. study. This means that the no effect dietary A1254 TRV for kit survival may be less than 1 mg/kg ww, and greater than 0.02 mg/kg ww (control), but more precise determinations cannot be made with the existing data.

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[9] Unfortunately, the statistical analyses in Lillie, et al. (1975) were only performed to compare the effects of different Aroclors (with the results of the multiple doses combined for any single Aroclor), or different doses (with the results of multiple Aroclors combined for any single dose). Statistical comparisons were not made to compare the effects of different doses of any single Aroclor.

Two studies, one performed with a commercial PCB product (Brunström, et al. 2001), and one with field-contaminated prey (Restum, et al. 1998), reported the reproductive effects of PCBs associated with exposures over both one and two breeding seasons. Restum, et al., also reported the reproductive effects in two generations of exposed females. Both studies showed increased adverse effects in the second year or generation of continuous exposure compared to the first (Figures 7-10, and 12). Brunström, et al. (2001) wrote:

> "In the second season, the effects on reproduction were more pronounced and clearly dose dependent... In our study, the concentration in the feed was the same during the two reproduction seasons, resulting in a reduced frequency of whelping females in the second season only. This finding suggests that the PCB concentration in the animals increased from the first to the second reproduction season, showing the relevance of long-term exposure for estimation of a LOAEL."

Brunström, et al. (2001) fed mink diets spiked with Clophen A50, one of the European commercial PCB products, and reported results for exposure over both 1 breeding season (6 months) and 2 breeding seasons (16 months). This study showed a dramatic decrease in the whelping frequency from 90 % of mated females for the first breeding season to 39 % for the second season in their "A50 high" treatment (2.3 mg/kg ww diet). The control whelping frequency was 93 % in both years. Live litter size per whelping female decreased nearly by half between the two exposure periods for the same treatment (from 3.8 live kits/whelped female the first year to 2.0 the second year) (control values 4.0 and 4.4, respectively). Mean kit bodyweight also decreased for this treatment (from 7.9 g to 6.7 g) (control values 9.6 and 8.9, respectively). Only kit bodyweight was statistically discernible from the control in the first breeding season, but, in addition to kit bodyweight, both whelping frequency and live litter size per whelped female were also statistically discernible from control values in the second breeding season. Sufficient data are available to calculate TRVs for both exposure periods for the number of live kits per mated female [10] (Table 2 and Figure 7). The low effect TRV for exposure over 2 breeding seasons (1.3 mg/kg) is 0.42 of the corresponding TRV for 1 season exposure (3.1 mg/kg), and the 2-season no effect TRV (1.1 mg/kg) is 0.47 of the 1-season value (2.4 mg/kg).

Restum, et al. (1998) fed mink various proportions of field-contaminated carp from Saginaw Bay, Michigan, and reported results for exposures over 1 breeding seasons (6 months), 2 breeding seasons (16 months), or 2 generations (exposure *in utero* [11] followed by 12 months exposure) (Figures 8, 10, and 12). Six comparisons are shown in Table 1 between 1-season and 2-season or 2-generation TRVs for live kits per mated female, kit bodyweight, and kit survival. Note that for live kits per mated female, the ratios of 2-season or 2-generation responses divided by the 1-season response result in maximum ratios. This is because the 1-season live kit per mated female TRV cannot be interpolated (it is at a higher dietary concentration than the highest tested). Instead of making an uncertain extrapolation, the relative response at the highest dietary concentration tested is used for the 1-season low effect TRV (0.9 relative response at 1.0 mg/kg). Since the 1-season EC_{25} is at a dietary concentration greater than 1 mg/kg, the actual product of dividing the 2-season or 2-generation TRVs by the 1-

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[10] The data for live kit production for single-season exposure is supplemented with the results of a single Clophen A50 treatment (12 mg/kg) reported by Kihlström, et al. (1992).

[11] Maternal exposure for 6 months including pregnancy. *In utero* means "in the womb", in other words, before birth.

season TRV would be smaller than the ratios shown in Table 1 for live kit per mated female (0.39 and 0.28, respectively). There are no such issues for the other endpoints. Overall, the ratio of 2-season or 2-generation TRVs divided by 1-season TRVs ranges from <0.28 to 0.87 for the various endpoints in the Restum, et al., study (Table 1).

For the purposes of adjusting the single-season Aroclor TRVs so they will be protective for sustainable occupancy by mink for multiple years or generations at a given location, the 1-season TRVs are multiplied by the mean ratio of the 2-season or 2-generation low effect TRVs divided by the 1-season TRVs based on the studies by Brunström, et al. (2001) and Restum, et al. (1998). The mean ratio of the seven comparisons is 0.52, that is, on average, the low effect TRV for 2-seasons or 2-generations exposure is 52 % of the low effect TRV for 1-season exposure to PCBs. Accordingly, the single-season TRVs for A1242 and A1254 are multiplied by 0.52 to derive TRVs for long-term sustainability. By this approach, the A1254 low effect TRV is 0.6 mg PCB/kg ww diet for live kit production and kit bodyweight, the A1254 no effect TRV is 0.5 mg PCB/kg ww diet for live kit production, and the A1242 TRVs are 1.3 (no effect) to 1.4 mg/kg ww (low effect) for live kit production.

The more conservative TRVs of the ones calculated for mink in this effort–no effect of 0.5 and low effect of 0.6 mg/kg ww diet based on A1254–are recommended for risk assessment purposes to account for the increased toxicity of PCBs that occurs with bioaccumulation and trophic transfer (foodchain transfer from prey to predators), or additive effects of concurrent exposure to co-contaminants that act through the same toxicological mechanisms as PCBs (Section 6.2.1.1).

5.2 Chicken Studies

The results of chicken studies are shown in Figures 17-32. Dose-response relationships are evident for hatchability (Figures 17-24) and chick bodyweight (Figures 25-27). Two dose-response patterns are evident for the effect of A1242 on hatchability (Figure 18)–one based on 3 studies by two research groups [12] (Briggs and Harris 1972; Cecil, et al. 1974; Lillie, et al. 1974, 1975), the other on 1 study by a third research group (Britton and Huston 1973). Each of these response patterns is separately analyzed instead of attempting to choose between the research results. An effect on chick survival is apparent for A1248, but not other Aroclors at the doses tested (Figure 28). There are no consistent dose-response relationships for egg productivity (Figure 29) or egg fertility (Figure 30). Although trends are apparent for chick deformities, studies were not performed at doses sufficiently high to allow interpolation of ED_{25}, except for the field study using field-contaminated feed (Figure 31) (studies based on field contamination are not used for TRV derivation). Only single data points are available for egg concentration and chick survival for each of the Aroclors considered in this effort (Figure 32), so concentration-response relationships cannot be evaluated precluding TRV derivation.

The interpolated TRVs are given in Table 3. The bodyweight-normalized dose TRVs (mg/kg_{BW}-d) are as follows: A1242–0.1-0.5 (no effect) to 0.4-0.8 (low effect) for hatchability, and 0.2 (no effect) to 0.9 (low effect) for chick bodyweight; A1248–0.4 (no effect) to 0.5 (low effect) for hatchability, 0.2 (no effect) to 0.6 (low effect)

[12] Two papers report data from the same experiment (Cecil, et al. 1974 and Lillie, et al. 1974).

for chick bodyweight, and 0.2 (no effect) to 0.3 (low effect) for chick survival; and A1254–0.6 (no effect) to 1.2 (low effect) for hatchability.

The interpolated egg TRVs (mg/kg whole egg, ww) are as follows: A1242–1.0 (no effect) to 1.5 (low effect) for hatchability, and 3 (no effect) to 10 (low effect) for chick bodyweight; A1248–0.7 (no effect) to 1.3 (low effect) for hatchability; and A1254–9 (no effect) to 12 (low effect) for hatchability.[13]

Although the lowest TRVs for hen dose are for A1248 and chick survival, little confidence can be placed in the calculated ED_{10} or ED_{25} because the interpolations are performed over a 10-fold dose gradient (Figure 28). Based on the shapes of the better defined dose-response plots for other endpoints, the interpolated values are probably underestimated. A similar concern applies to the no effect TRVs for A1242 or A1248 doses and chick bodyweight (Figure 25). Since two dose-response patterns are evident for A1242 and hatchability (Figure 18), the recommended bird TRVs are based on A1248 and hatchability–0.4 mg/kg_{BW}-d (no effect) and 0.5 mg/kg_{BW}-d (low effect) (bracketed by the two A1242 values).

For egg TRVs, the best defined concentration-response plots are for A1242 and hatchability (Figure 22) and A1254 and hatchability (Figure 24), in which interpolations are performed within gradients of 2-fold or less. Although the egg TRVs for A1242 chick bodyweight are interpolated over a 7-fold concentration gradient (Figure 27), and combines disparate exposure routes (egg injection and contaminant transfer from exposed hens), the low effect TRV is very close to the treatment mean based on dosed hens and not significantly influenced by the egg injection study (the converse is true for the no effect TRV). The egg TRVs for A1248 and hatchability are interpolated over a 7-fold concentration gradient (Figure 23), and therefore are have greater uncertainty than the A1242 or A1254 TRVs for the same endpoint. The recommended egg TRVs are based on the more sensitive of the Aroclors with well-defined concentration-response plots, that is, A1242 and hatchability–1.0 (no effect) to 1.5 mg/kg ww whole egg (low effect).

6 Uncertainty

Uncertainty is discussed for the method for deriving the TRVs and the application of the TRVs for risk assessment.

6.1 TRV Uncertainty

6.1.1 Confounding Factors

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[13] Adverse effects have been reported at whole-egg concentrations greater than 4 mg/kg based on the A1254 study by Tumasonis, et al. (1973) in reviews by Barron, et al. (1995) and Hoffman, et al. (1996), which is lower than the egg A1254 TRVs presented here also based in part on Tumasonis, et al. (1973). The difference is that the treatment response used in the present effort is based on the effects occurring during exposure to PCBs (maximal suppression of hatchability at 100 mg/kg in yolk). Tumasonis, et al. (1973) also reported deformities in chicks at yolk concentrations at or above 10-15 mg/kg in the weeks following cessation of exposure to PCBs, which is the basis for the effect levels reported in the reviews. These data were not used in the present effort because the effects occurred after cessation of exposure, and quantitative data on deformity rates were not provided.

An important potential source of uncertainty is associated with combining the results of separate studies together into aggregated dose-response plots because the studies were not performed under standardized protocols. Differences in results between studies may have occurred that are not linked to treatment doses for several reasons including differences in rearing conditions, feed, animal strains, health or nutritional status, age, exposure routes, or exposure durations. Other possible confounding factors include unsuspected alternate sources of contamination in the feed, water, or experimental facility (either to the same chemical being tested or to another unmeasured chemical), or differences in the composition of the Aroclor batches tested (different lots of the same Aroclor may differ in toxicity due to fluctuations in the composition of toxic PCB congeners or co-contaminants formed during manufacture).

The significance of these potentially confounding factors is assessed by examination of the dose-response plots of the combined studies. Marked deviations from interpretable dose-response patterns indicate that study results are incompatible for some reason. An interpretable dose-response pattern is one that is consistent with known patterns and toxicological theory. The basic pattern is a sigmoid curve in which low doses have minor effects, higher doses exhibit increasingly adverse effects, and the effects at the highest doses asymptotically approach maximum adversity. Two modifications are threshold models, in which increases in dose at low dose levels cause no significant changes in response until a threshold dose is reached, above which the sigmoid pattern applies, and hormetic models, in which doses lower than a threshold for adverse effects show an enhanced (positive) response. Of the endpoints considered in this effort, only two exhibit uninterpretable dose-response patterns–A1254 and egg productivity (Figure 29) or fertility (Figure 30). Either A1254 has no effect on egg productivity or fertility (at the doses tested), or the studies combined into these plots are incompatible for one or more of the factors described above. Regardless of the reason, these endpoints are excluded from the TRV process. Chick survival is also excluded because there are insufficient data to reveal dose-response patterns for any Aroclor (Figure 32). The rest of the endpoints of studies performed with commercial PCB products exhibited interpretable dose-response patterns consistent with one of the models described above, which indicates that the results of the combined studies were not significantly affected by confounding factors (with the possible exception of A1242 and hatchability discussed below).

6.1.2 Exposure Duration

In addition to the overall screening of interpretable dose-response patterns, it is also possible to specifically assess the possible effects of combining studies with different exposure durations or exposure routes. It is not feasible to exactly match the exposure durations between the studies combined into single plots. Exposure duration ranged from 6 to 14 wk for chicken feeding studies (most between 6 and 9 weeks), and from 3 to 10 months for mink studies performed over a single breeding season. The data are consistent within the range of exposure durations of the combined studies as discussed below.

The studies combined for A1248 and hatchability have similar exposures durations–8 (Lillie, et al. 1975) and 9 wk (Lillie, et al. 1974; Cecil, et al. 1974; Scott 1977)–and exhibit a consistent dose-response pattern (Figure 19). Three studies were combined to evaluate the effect of A1254 on hatchability with exposure durations of 6 (Tumasonis, et al. 1973), 9 (Lillie, et al. 1974 and Cecil, et al. 1974), and 14 wk (Platanow and Reinhart 1973); however, the relative response plots show internally consistent responses (no obvious duration effects) on the basis of either hen dose (Figure 20) or egg concentration (Figure 24). This is partly because the shortest duration

treatment (6 wk) was at a high dose that completely suppressed hatchability, but mainly because the results of the 9- and 14-wk studies are remarkably consistent. At first impression, the divergent A1242 and hatchability patterns appear to be related to exposure duration (Figure 18). The pattern showing greater toxicity is largely based on 8- to 9-wk durations (Lillie, et al. 1974, 1975; Cecil, et al. 1974), and the one showing lesser toxicity on 6-wk duration (Britton and Huston 1973), except that the data by Briggs and Harris (1972) with 6-wk exposure is consistent with the pattern exhibited by the 8- to 9-wk exposure studies, and inconsistent with the Britton and Huston study. The divergent A1242 patterns are inexplicable with the available information and therefore are separately assessed. This uncertainty is reflected in the TRV ranges presented for A1242 dose and hatchability.

All of the mink Aroclor feeding studies were performed over single breeding seasons. Three studies are combined for A1242 and live kit production (Figure 2) with rounded exposure durations of 5 (Käkelä, et al. 2001), 8 (Bleavins, et al. 1980) and 10 months (Aulerich and Ringer 1977). No and low effects are bracketed by the hormetic response at 2 mg/kg ww dietary concentration (Aulerich and Ringer 1977) and complete reproductive suppression at 5 mg/kg (Bleavins, et al. 1980) with roughly comparable exposure durations. The treatment at an intermediate dietary concentration (3 mg/kg) has the shortest exposure duration of the combined studies (5 months), which was terminated at the onset of breeding (Käkelä, et al. 2001) in contrast to the other studies, but exhibits a response consistent with the longer duration studies (in fact, plots close to a direct log-linear line between the other studies). Again, there is no evidence that the difference in exposure durations among studies has distorted the concentration-response relationship. Three studies are combined for A1254 and live kit production (Figure 3) with four rounded exposure durations of 3 (Kihiström, et al. 1992), 4 (Aulerich and Ringer 1977), 6 (Wren, et al. 1987), and 10 months (Aulerich and Ringer 1977). Live kit production is almost completely suppressed at all the tested dietary concentrations of 2 mg/kg or greater (3-, 4-, and 10-month exposure durations). An apparent inconsistency occurs at 1 mg/kg, with a 6-month exposure study exhibiting hormesis (Wren, et al. 1987) and a 4-month exposure study showing adverse effects (Aurlerich and Ringer 1977), which are the opposite trends expected based solely on the respective exposure durations (the data are smoothed at this dietary concentration by averaging the two responses). However, since reproduction is unsuccessful at 2 mg/kg (the sole live kit in that treatment soon died), there is no margin for increasing the A1254 low effect TRV, that is, it must be less than 2 mg/kg ww diet (for a single breeding season). The A1254 TRVs might be overestimated (too high) because they are bracketed at the no-effect side by the results of shorter exposure durations (4 to 6 months), that is, greater adverse effects may occur if mink were exposed to 1 mg/kg for 10 months instead of 4-6 months. The same consideration applies to the low effect TRVs for A1254 and kit bodyweight (Figure 5), which is bracketed by a 10-month exposure study for severe effects and a 6-month exposure study for lesser effects. However, a similar disparity in exposure durations of A1242 studies did not result in an obvious inconsistency in responses.

Two studies are combined for one of the Clophen A50 endpoints (live kits per mated female), with exposure durations of 3 (Kihlström, et al. 1992) and 6 months (Brunström, et al. 2001) (Figure 7). The responses are consistent because the single 3-month exposure treatment was performed at a sufficiently high dose to completely suppress reproduction. Once maximum adversity occurs, there is no scope for further change in response with increased exposure duration.

In contrast to the generally consistent results of combining single breeding season studies of varying exposure durations, exposure duration effects are apparent in both of the studies that included continuous exposures over

both 1 breeding season and 2 breeding seasons or 2 generations (Figures 7-10 and 12). The exposure duration was 6 months for the single breeding season treatments in both studies, and was 16 (Restum, et al. 1998) and 18 months (Brunström, et al. 2001) for females continuously exposed over 2 breeding seasons. The second generation females were exposed in the womb (6-month maternal exposure) followed by 12 months postnatal exposure (Restum, et al. 1998). The effect may be more pronounced for live kit production and possibly kit survival compared to kit bodyweight (compare Figures 7 with 9, and 8 or 12 with 10), and appears to be more pronounced for exposure over 2 generations compared to the same adult female continuously exposed over 2 breeding seasons (Figures 8, 10, 12). Since the concentration-response patterns differ for exposures over single versus double breeding seasons or generations, the data are not aggregated.

To summarize, there is no evidence that the range of exposure durations of the studies combined for assessing effects during single breeding seasons resulted in significant inconsistencies in the dose-response patterns for either chicken or mink. The A1254 TRVs for mink might be overestimated (too high) because the effect sizes for live kit production and kit bodyweight are bracketed by shorter exposure duration studies on the no effect side (4 to 6 months) as compared to the severe effect side (10 months), however, a similar disparity for A1242 showed no inconsistencies (a 5-month exposure duration treatment is intermediate in both dietary concentration and response to 8- to 10-month treatments). However, two studies show that the responses to 6-month exposures during a single breeding season differ from the responses to continuous 16- to 18-month exposures over two breeding seasons, and therefore should not be combined into aggregated dose-response plots. Similarly, a study shows that the responses to exposure over a single breeding season should not be aggregated with the responses of females exposed *in utero* followed by 12 months postnatal exposure.

6.1.3 Exposure Route

The same approach can be used to assess the effect of different exposure routes. The exposure route for all of the mink studies was the same, that is, through contaminated diet. For oral dose to chicken, the exposure route was contaminated diet with one exception–contaminated water in the study by Tumasonis, et al. (1973). The data do not show an effect related to this difference in exposure media. The response due to exposure to contaminated water is consistent with the effect trends of exposure to contaminated diet (Figures 20 and 24). For egg concentration, the exposure route was through hen dietary exposure except for Gould, et al. (1997) in which PCBs were injected into egg yolks. The Gould, et al. study influenced one TRV (A1242 egg residue and chick bodyweight), for which the egg injection data are combined with a single treatment from a hen feeding study (Lillie, et al. 1974, Cecil, et al. 1974) (Figure 27). In addition to the difference in exposure route, the relative "chick" bodyweight for Gould, et al. (1997) is based on 17-d embryos, not on hatched chicks. However, the response trend is reasonably consistent between exposure routes, or, better put, there is no obvious inconsistency between the response of the two studies. In any case, because of the spacing of the treatments, the low effect egg A1242 TRV for chick bodyweight is predominantly influenced by the hen feeding treatment, and the no effect TRV by the egg injection study. This means that the no effect egg TRV for A1242 and chick bodyweight may be less certain in comparison with the low effect TRV.

6.1.4 Linear Interpolation

The appropriate regression technique is a source of uncertainty for the ED_x procedure because the results depend on how well the dose-response relationship is modeled (Section 3). Model uncertainty in the present effort is minimized in three ways. 1) Uncertainties related to characterization of complex dose-response relationships, such as threshold or hormesis models, are avoided by linear interpolation of TRVs between the treatments that bracket the selected effect sizes for no and low effects. It is not necessary to mathematically represent the entire dose-response curve to calculate the ED_{10} or ED_{25}, so long as the overall shape of the dose-response relationship conforms with one of the known patterns. Related to this, extrapolation beyond the empirical data is strictly excluded. 2) The effect sizes (10 % decrease from control for no effect, and 25 % decrease for low effect) are selected to minimize model dependence (Section 3). 3) The results of linear interpolations are only accepted when performed within the steep linear portion of the dose-response plots, and, related to this restriction, confidence in the TRVs interpolated between narrow dose gradients is greater (less uncertainty) than for TRVs interpolated between wider dose gradients. The Aroclor TRVs for mink are interpolated within 2-fold or less gradients in dietary concentration (A1242 or A1254 and live kit production, and the low effect A1254 TRV for kit bodyweight). Most of the bird TRVs are interpolated within 2-fold gradients in dose (A1242 or A1248 and hatchability) or egg concentration (A1242 or A1254 and hatchability), and one of the no effect TRVs for A1242 dose and hatchability is interpolated over a 3-fold gradient. This indicates that uncertainty related to appropriate characterization of the dose-response relationship is low.

Although the TRVs for A1254 dose and hatchability are interpolated over a 4-fold gradient, there is low model uncertainty for the low effect TRV because it coincides with one of the treatment means (Figure 20). However, there is greater model uncertainty for the no effect TRV for A1254 and hatchability because the shape of the dose-response relationship is uncertain over the 4-fold gradient. Similarly, the TRVs for A1242 or A1248 and chick bodyweight (Figure 25), or A1248 and survival (Figure 28) have high model uncertainty because they are interpolated over 10-fold dose gradients (although modeling uncertainty is appreciably less for the low effect TRV for A1242 and hatchability because the treatment mean plots close to the low effect size). Despite the apparent greater sensitivity of chick survival for A1248 (or the no effect TRV for chick bodyweight) compared to hatchability, the A1248 TRVs are based on hatchability because the modeling uncertainty is high for the other endpoints.

To summarize, modeling uncertainty is low for the final TRVs because they are interpolated over narrow dose gradients within well-defined dose-response relationships.

6.1.5 Adjustment of Mink TRVs for Exposure Over 2 Breeding Seasons or 2 Generations

Another source of uncertainty for the mink TRVs concerns the empirical observations that continuous exposure over 2 breeding seasons or 2 generations increases the severity of the reproductive effects of PCBs compared to exposure over a single season, "showing the relevance of long-term exposure for estimation of a LOAEL" (Brunström, et al. 2001). Since the effect has been observed in mink feeding studies both with controlled dosing with one of the European commercial PCB products and with field-contaminated fish from a site in the United States, it is unlikely that it is caused by some unique attribute of the European product or some non-PCB-related contaminant in the field-contaminated fish (also, the field-contaminated fish of the latter study were collected at one time, homogenized, and stored for use throughout the study, so co-contaminant levels did not vary between breeding seasons). This indicates the increased toxicity of PCBs to mink with continuous exposures over

multiple breeding seasons or generations may be a general characteristic of PCBs, with implications for long-term occupancy of contaminated sites.

The potential for increased PCB toxicity with extended exposure is relevant for assessing the long-term suitability of habitats for mink because the estimated longevity in the wild is 3 to 6 years, with maximum longevity of 8 to 12 years during which mink are fecund for 7 or more years (Chapman and Feldhamer 1982; Merritt 1987). Unfortunately, mink Aroclor studies have only been performed for single breeding seasons and single generations, so there is uncertainty in either accounting for or ignoring the increase in toxicity associated with exposures over 2 breeding seasons or 2 generations in other studies. If excluded, a habitat remediated on the basis of single-breeding season TRVs may allow for unimpaired mink reproduction during the initial year of occupancy, but not in succeeding years or generations of continued occupancy. The net effect would be that only transient mink would have unimpaired reproduction, but not resident mink that remain in the same locality through multiple years or generations. In other words, the habitat might remain a population sink in which the presence of mink would depend on regular immigration from other areas. If the increase in toxicity related to exposure over multiple years or generations is accounted for by adjusting the single-season TRVs, reproductive impairment by PCBs would not be expected in mink regardless of residence time or number of generations at the site. The uncertainty in this scenario is in determining the appropriate adjustment to Aroclor TRVs when the empirical data are limited to Clophen A50 and field-contaminated fish.

The uncertainty in not making this adjustment would be low if the difference between the effects of exposures to 1 versus 2 breeding seasons or generations was relatively small. However, the study with Clophen A50 showed large decreases in the proportion of females giving birth (57 % decrease in whelping frequency) and the number of live kits per whelped female (47 % decrease) compared to exposures over 1 breeding season (Brunström, et al. 2001), so that only one-fourth of the number of live kits were produced per mated female in the second breeding season compared to the first (Figure 7). The Restum, et al. (1998) study with field-contaminated fish showed similarly large effects for live kit production (Figure 8) and kit survival (Figure 12), as well as a pronounced effect on the bodyweight of kits whelped by 2nd generation females (themselves exposed *in utero* and postnatally) much greater than the effect on kit bodyweight due to exposure to adult female mink over either 1 or 2 breeding seasons (Figure 10).

The weight of evidence indicates that the uncertainty associated with excluding an exposure duration or generational effect may be high, that is, potentially severe adverse effects may be overlooked. However, there is a large range in the ratio of 2-season or 2-generation exposure-based TRVs divided by 1-season exposure TRVs for the various endpoints reported in the two studies, from less than 0.3 to 0.9 (Table 2), which means that selection of an adjustment factor for Aroclor TRVs is correspondingly uncertain. Although the ratios are lowest for live kit production (<0.3-0.4) and kit bodyweight of 2nd generation-exposed females (0.4), the two endpoints used for the mink Aroclor TRVs, the approach taken in this effort is to use the mean ratio of all the endpoints for which low effect TRVs could be calculated (mean of 0.52, n = 7). The mean ratio should have lower uncertainty compared to ratios selected from either end of the range, and is therefore used to adjust the mink Aroclor TRVs in the absence of Aroclor-specific data.

For comparison, the mink TRV for the GLI water quality criteria is based on an A1254 dietary LOEC of 2 mg/kg (Aulerich and Ringer 1977), which was converted to a NOEC of 0.2 mg/kg by dividing by an uncertainty

factor of 10 (USEPA 1995a). These values bracket the mink A1254 TRVs derived in this effort. The low effect dietary TRV of 0.6 mg/kg is significantly lower than 2 mg/kg, but, as discussed in Section 3, the LOEC used by the GLI resulted in complete reproductive suppression, therefore the actual lowest dietary concentration associated with the onset of adverse effects is expected to be lower than 2 mg/kg. Since the LOEC resulted in severe effects, the NOEC for the GLI (the sole basis for decision-making in the GLI effort) was conservatively estimated by using a large uncertainty factor, which resulted in a value somewhat lower than the no effect dietary TRV of 0.5 mg/kg based on long-term sustainability. This comparison indicates that an appropriate level of conservatism was used in the GLI effort in estimating a no effect level from less than ideal toxicity data, and that the TRVs derived in this effort are reasonably consistent with the GLI even though the values are adjusted to account for the observed increase in toxicity with continuous exposure over multiple years or generations.

6.1.6. Endpoints and Effect Size

Consistent with the guidance for ecological risk assessment in the Superfund program (USEPA 1997), the toxicological endpoints included in this effort are one that could impact populations–live kit production, kit survival, and kit bodyweight for mink; and hatchability, deformities, chick survival, and chick bodyweight for birds (bodyweight is an indicator of the potential for long-term survival). The main uncertainties with the toxicological endpoints relied on for the TRVs are that data are insufficient for fully evaluating all of the considered endpoints, for example, kit or chick survival might be a more sensitive endpoint than live kit production or hatchability; and data are sparse for other endpoints that could impact populations, such as immune system effects, or neurological or other somatic effects that could impair performance of essential activities such as mating, rearing, hunting, evading predation, migrating, or competing with other species. A possible field example involves Caspian tern exposure to PCBs at Saginaw Bay, MI. Although productivity did not appear to be affected by exposures, elevated plasma PCB level was associated with decreased return of adults to the colonies, suggesting a possible effect on survival (see discussion and references in Hoffman, et al. 1998). The possibility that other endpoints might be more sensitive or result in greater overall impact in the field compared to the endpoints used for TRV derivation in this effort (live kit production, kit bodyweight, and hatchability) is an underlying uncertainty.

The effect sizes used in this effort are chosen for pragmatic reasons–to minimize model dependence, approximate the power of well-designed toxicity studies, and maintain general consistency in approach with other regulatory uses of toxicity test data (Section 4.2). The main uncertainty with the effect size selection is that they are not linked to population models, that is, the effects of 10 or 25 % decrements in hatchability, live kit production, or kit bodyweight on local populations are not explicitly modeled. There is uncertainty in both directions–a 10 % decrease may result in larger impacts than appropriate for a no effect level, or a 25 % decrease may not result in discernible impacts. As discussed in Section 4.2, this uncertainty is low because of the very steep slope of the dose-response relationship between no effects and severe effects–mostly separated by less than 3-fold gradients in dose or dietary concentration. Since population modeling is irrelevant for either zero impacts or 100 % adverse impacts (the local population will not be impacted by exposures that do not affect individuals, but is clearly not sustainable when reproduction is completely suppressed), modeling could only influence the TRVs within the 2- or 3-fold gradient between the extremes in response.

Such modeling for mink or bird populations would itself have large uncertainty associated with it. There are multiple sources of uncertainty in modeling or measuring population responses to stresses (Lester, et al. 1996; Power, 1997; NRC 1998; Rose 2000; Forbes, et al. 2001; Shea and Mangel 2001; Tyre, et al. 2001). A significant uncertainty in choosing effect sizes based on population models is that "simple, general, *a priori* predictions are not feasible" even with knowledge of life history dynamics and how life history traits are affected by toxicant exposure, because of the large number of factors influencing the outcome (Forbes, et al. 2001). Uncertainty is further increased because exposure to new stressors can change which population traits most influence population growth rates (referred to as "vital rates"). This means that identification of sensitive population traits with prospective demographic studies (prior to exposure to stressors) does not reliably predict which population trait is most important for population impacts following exposure (Cooch, et al. 2001 and references).

> "[T]he vital rate which contributes most to the observed variability in life histories is not necessarily the one to which life histories are most sensitive (which is revealed by the prospective analysis), nor the one that will necessarily make the biggest contribution to variability in another environment. This is especially true in wild populations, where natural selection is likely to minimize variation in those parameters to which population growth (i.e., fitness) is potentially the most sensitive, such that observed variation in growth over time might be reasonably expected to reflect changes in one or more of the parameters to which growth is less sensitive." [citations omitted] (Cooch, et al. 2001).

Exposure to toxic chemicals not only "switches the sensitivity of [population growth rate] to changes in vital rates", but also "increases the sensitivity of organisms to stressors that affect vital rates other than the ones that have been affected by the toxicant" (Kammenga, et al. 2001). An additional uncertainty in identifying sensitive population traits is that the results depend on both the spatial and temporal scales of the assessment (Power 1997; Rose 2000). These considerations mean that there is large uncertainty in applying general population models, and significant uncertainty may be associated even with species- and site-specific models because contaminant exposure may change the interactions between the various population traits and population growth, that is, the pre-exposure demographic model may not apply to post-exposure conditions.

Since the PCB dose-response relationships show a narrow range between the onset of adverse effects and maximum severity, the uncertainty associated with population modeling to refine the choice of effect size for determining TRVs is considered excessive relative to the constrained range over which the TRVs can vary.

6.2 Application Uncertainty

There are several sources of uncertainty associated with the application of the TRVs to field situations. In addition to the usual uncertainties of extrapolating from laboratory studies to field conditions, and, in the case of the bird TRVs, extrapolating between species, there are additional uncertainties associated with measuring PCBs as Aroclors in environmental samples, or measuring or estimating TEQ, and their use in risk assessments.

6.2.1 PCBs and Risk Assessment

Polychlorinated biphenyls (PCBs) are not a single chemical, but are mixtures of large numbers of different chemicals based on a common structure–a biphenyl "frame" with variable numbers of chlorine atoms attached to it. Each different arrangement of the number of chlorine atoms and their spatial position on the biphenyl is a separate PCB chemical, referred to as a "congener". There are 209 possible PCB congeners, each with slightly to very different chemical, physical, and toxicological properties. The complex mix of congeners with differing properties presents several challenges for assessing the risks of PCB exposures.

First, the toxicity of PCBs is caused by a subset of the congeners. The best understood subset is the dioxin-like congeners that act wholly or in part through the same mechanism as dioxin (Van den Berg, et al. 1998). The dioxin-like congeners, often referred to as "planar" or "coplanar" congeners, are capable of binding with the same cellular protein--aryl hydrocarbon receptor (AhR)–that binds with dioxin in the initial step of a cascade of interactions leading to expression of toxic effects. However, some of the non-coplanar, non-dioxin-like PCB congeners or their metabolites also have toxic effects through separate toxic mechanisms that are not as well understood (Fisher, et al. 1998). Some of the coplanar congeners may act through multiple pathways, that is, they may contribute to both dioxin-like and non-dioxin-like toxicity. The combined toxicity of the dioxin-like congeners can be estimated through a toxic equivalent (TEQ) approach (described below), but, at present, there is no comparable approach for estimating the combined effect of non-dioxin-like congeners.

Second, each of the different commercial PCB products are comprised of different proportions of congeners, which means that the toxicity varies for the different Aroclors, for example, A1242 is more toxic than A1260 because A1242 has a higher proportion of dioxin-like congeners. The uncertainty related to differences in congener composition between Aroclors is addressed in this effort by separately assessing the toxicity of each Aroclor. The toxicity of a European product (Clophen) is assessed separately from American products (Aroclors) for the same reason.

Third, once released into the environment, the differences in the chemical and physical properties of the congeners result in differences in their fate and transport, that is, in their persistence, how they move through the environment, and in which components they are likely to accumulate in greater concentrations. For example, the lower chlorinated congeners (ones with few chlorine atoms) volatilize (evaporate), solubilize (partition to water), and degrade more readily so they tend to decrease over time, while the heavier, more chlorinated congeners are less volatile, less soluble, often less readily degraded, and therefore are more persistent in the environment. Conversely, under anaerobic conditions (without free oxygen), some of the higher chlorinated congeners may be more readily degraded than lower chlorinated ones. Therefore, congener composition of PCBs in the environment can change over time, a process described as "weathering". The congener composition may also be altered as PCBs are passed through foodchains, that is, the congener pattern retained in animals may differ from the pattern in their food. The changes in congener proportions mean that the toxicity of PCBs in the environment differs from the toxicity of the source Aroclors depending on the type and degree of weathering and bioaccumulation.

6.2.1.1 Aroclor-based Risk Assessment

The original toxicity testing of PCBs was performed with commercial Aroclors, with the results presented in terms of Aroclor dose or concentration. An advantage of the Aroclor approach is that studies show the

combined effects of all the toxicological modes of actions of the various congeners (both dioxin-like and non-dioxin-like) and manufacturing impurities, and their net interactions (additive, synergistic, and antagonistic). This means that, for exposures to tested commercial PCB products that have not been significantly weathered, there is little uncertainty related to multiple toxic mechanisms or interactions among congeners or other co-contaminants formed in the PCB manufacturing process. Also, there is a large ecotoxicological database for Aroclor effects.

The main uncertainties of Aroclor-based risk assessment are related to the changes in congener composition following release to the environment (weathering and bioaccumulation), which can affect measurements of PCB levels and estimations of risk. Various methods have been used to determine the amount of PCBs in a sample as a concentration of an Aroclor or a mix of Aroclors (summarized in Eisler and Belisle 1996). Uncertainty is introduced because the congener composition of environmental samples may differ from that of any particular Aroclor or combinations of Aroclors, which results in larger variability in analytical results between laboratories than is usual for other chemical analyses. In formal terms, measurement error is larger for Aroclor analyses compared to congener-specific analyses.

Changes in congener patterns also can affect toxicity. Loss of lower chlorinated congeners to volatilization or degradation can increase the proportional dioxin-like toxicity of the remaining PCBs because many of the dioxin-like congeners are persistent. Anaerobic degradation may reduce toxicity due to higher chlorinated dioxin-like congeners, although the products may also be toxic (e.g., Ganey, et al. 2000). Foodchain transfers may increase the toxicity of the PCBs retained in organisms (see references in Lugwig, et al. 1996). For example, the biomagnification factors (BMF) for dioxin-like congeners are twice as high as the BMFs for total PCBs in zooplankton or *Mysis* (a freshwater invertebrate) feeding on phytoplankton, or *Diporeia* (another invertebrate) feeding on *Mysis* (Trowbridge and Swackhamer 2002). This preferential biomagnification increases the toxicity of the PCBs in the organism relative to the source PCBs because of the increased proportion of dioxin-like congeners accumulated in their tissues. Since the organisms in this example are representative of the base of an aquatic foodchain, the altered pattern with increased toxicity will be passed to animals feeding on zooplankton or aquatic invertebrates. This is evident in one study of animals that feed on plankton, the sediment-to-biota BMF for bioassayed TEQ was 10 times greater than the BMF for PCBs (Jones, et al. 1993). There is inconsistent evidence for preferential biomagnification of dioxin-like congeners by piscivorous (fish-eating) fish (Jones, et al. 1993; Metcalfe and Metcalfe 1997), but marked preferential biomagnification of dioxin-like congeners has been reported in some studies of piscivorous birds (gulls and cormorants) and mammals (otters) (Koslowski, et al. 1994; Guruge and Tanabe 1997; Leonards, et al. 1997). In general, risk assessments based on the original source Aroclor are likely to underestimate the risk of bioaccumulated PCBs (Ludwig, et al. 1996; Giesy and Kannan 1998).

Another potential source of uncertainty in Aroclor-based assessments is that total risk in the field may be underestimated because the approach does not readily allow for combined assessment of the effects of PCBs and additional contaminants with the same toxicological mode of action. For example, contributions to dioxin-like toxicity may be made by dioxins, polychlorinated dibenzofurans, and other chemicals in addition to PCBs. The source of the additional chemicals may be from the same facility that released PCBs or from separate sources (either local or distant through atmospheric transport). Regardless of the sources, the presence of additional chemicals with dioxin-like activity in the field reduces the amount of PCB exposure that can be tolerated by

wildlife in comparison to controlled exposures to commercial PCB products in captive animals not simultaneously exposed to additional dioxin-like chemicals.

6.2.1.2 Dioxin Toxic Equivalent-based Risk Assessment

Another approach for assessing the risks of PCBs is based on the total dioxin-like effects (TEQ), either calculated from congener-specific analytical data or measured by *in vitro* bioassays. Some advantages of these approaches are that they are not subject to the analytical uncertainties related to the potential mismatches between Aroclor standards and weathered PCBs, they facilitate assessment of the combined toxicity of dioxin-like PCB congeners and other dioxin-like contaminants, and TRVs can be based on studies of any chemical with dioxin-like toxicity when the results are given as TEQ (in contrast to Aroclor-specific results, which can not be generalized to other dioxin-like chemicals).

The main uncertainties associated with the currently available TEQ approaches for risk assessments are related to the methods used to determine the TEQ, and the potential significance of non-dioxin-like effects.

One TEQ approach is based on congener-specific analytical data in which the concentration of each dioxin-like congener is multiplied by its toxic equivalency factor (TEF), the fractional toxicity of that congener compared to 2,3,7,8-TCDD, which are summed for all dioxin-like congeners to give the toxic equivalent concentration (TEQ). By this approach, TEQ represents the concentration of the most toxic dioxin congener that is expected to equal the potency of the mix of PCB congeners in the sample. The approach permits inclusion of additional chemicals with dioxin-like potency such as polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans.

An obvious source of uncertainty are the TEF values. The current consensus TEFs are "order of magnitude estimates of the toxicity of a compound relative to TCDD" based on a tiered evaluation of the relative potencies (REPs) reported in a variety of studies (Van den Berg 1998). The order of magnitude estimate is an "illustration of the overall uncertainty in TEF values based on the differences in outcomes of the different end points and the variation in available data for the different congeners" (van Leeuwen 1999). Another indication of TEF uncertainty is the difference in TEF schemes by different groups and at different times, which also limits the usability and comparability of TEQ studies unless the full congener data were reported so that results can be converted to a common basis (Dyke and Stratford 2002). Another source of uncertainty is the additivity assumption in the TEQ calculation. Although dose additivity is supported by many studies (Van den Berg 1998), non-additive interactions also are reported. These uncertainties are believed to be less than the level of uncertainty associated with Aroclor-based assessments, supported by examples of good correlations in practice between TEQs and toxic effects (Van den Berg 1998; van Leeuwen 1999; Birnbaum 1999; Tillitt 1999), however, caution has also been expressed for the use of the TEF approach for PCBs based on "nonadditive interactions, coupled with the unusually broad range of TEF values observed for some PCB congeners" (Safe 1998). An uncertainty related to analytical issues is that most of the dioxin-like PCB congeners occur in very low concentrations, which means that measurement errors of congeners with high TEF values will be magnified in TEQ calculations. An extreme example in a recent study is unuseable analytical data for congener 126 due to interference (Trowbridge and Swackhamer 2002). Since congener 126 is often one of the greatest contributors to the TEQ of PCBs, the calculated TEQs of this study are underestimated and inappropriate for risk assessment

purposes.[14] Since the TEFs for different dioxin-like congeners vary by several orders of magnitude, small measurement errors for highly potent congeners can result in large errors in TEQ calculations. Another uncertainty is that TEFs are not presently available for all chemicals with potential dioxin-like activity, although TEFs are available for the ones shown to account for the majority of the dioxin-like toxicity in intact animals.

Another approach for determining TEQs is by *in vitro* bioassays, in which the response of cultured cell lines exposed to dioxin-like chemicals is measured. An advantage of the bioassay approach is that it provides an integrated measure of the effects of all the chemicals in a mixture that affect dioxin-like responses with all of their interactions (additive, synergistic, and antagonistic). Interactions can occur between dioxin-like chemicals or with non-dioxin-like chemicals that modulate dioxin-like responses. The main uncertainties are related to interspecific differences in cell responses, and issues involved in extrapolation of effects in isolated cells to intact animals. Cells of different species show differences in interactive effects between PCB congeners. For example, at high doses, PCB congener 52, one of the di-*ortho*-substituted congeners [15], inhibits cellular responses to dioxin or dioxin-like PCB congeners in bioassays performed with mouse and rat cell lines, but not with guinea pig or human cell lines (Aarts, et al. 1995). This means that the presence of di-*ortho*-substituted congeners in Aroclors may reduce the TEQ measured in bioassays performed with cultured mouse or rat cell lines (reportedly by as much as 2 orders of magnitude in comparison with a calculated TEQ that assumes additivity, see references in Aarts, et al. 1995), but not in bioassays performed with cultured guinea pig or human cell lines. In addition to measurement uncertainties related to interspecific differences in cellular responses, there are uncertainties related to extrapolation of *in vitro* responses of isolated cell cultures to *in vivo* [16] responses of intact animals. One of the advantages of bioassays–an integrated response to direct administration of complex environmental mixtures to cells–also introduces uncertainty because the dosing does not reflect the pharmacokinetics [17] in intact animals. Although many chemicals are capable of binding with the Ah receptor, their ability to cause dioxin-like toxicity also depends on their pharmacokinetic behavior, for example, how rapidly they are metabolized (degraded) (Birnbaum 1999) or distribution patterns within an animal (for examples of species differences in PCB distribution among organs see Bachour, et al. 1998). *In vitro* bioassays may therefore show responses to chemicals that have little or no effect in intact animals.

> "In summary, a single *in vitro* assay based on a single surrogate species may not accurately predict the toxicity of a chemical or complex mixture following exposure to other species.

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[14] The purpose of this particular study was to investigate the transfer of PCB congeners through selected trophic levels in an aquatic ecosystem, for which the loss of data for a single dioxin-like congener is not crucial. However, a similar data gap would be unacceptable for a risk assessment.

[15] Di-*ortho*-substituted congeners have 2 chlorine atoms attached in the positions closest to the bond that holds the biphenyl "frame" together, with variable numbers of chlorines attached at other positions. The 2 *ortho* chlorines prevent these congeners from taking on the planar configuration necessary for activating the Ah receptor, and therefore they do not exhibit dioxin-like toxicity, but, at high concentrations, inhibit the Ah receptor (with varying efficiency in different species) so that it becomes less responsive to dioxin-like congeners.

[16] *In vivo* means "in the living", and refers to experiments performed with intact living organisms.

[17] Pharmacokinetics refer to the rates of various processes that affect the movement and form of chemicals in living organisms including uptake, distribution, binding, biotransformation, and elimination.

> Nevertheless, the use of *in vitro* assays provides a general tool as a prescreening method of TEQs in environmental samples. However, it does not replace *in vivo* experiments when determining TEFs for dioxinlike compounds." (Van den Berg, et al. 1998).

Another source of uncertainty for TEQ-based risk assessments is that the current approach does not include non-dioxin-like toxicity (by definition). Non-dioxin-like toxicity, that is, toxic effects not mediated by the Ah receptor, may be induced by non-coplanar PCB congeners (Fisher, et al. 1998), or biotransformed PCB products such as hydroxylated metabolites (Schuur, et al. 1998) or methylsulfonyl metabolites (Johansson, et al. 1998). The uncertainty would be low if the thresholds for non-dioxin-like effects are lower than for dioxin-like effects, in which case assessments based on dioxin-like effects would be protective for all adverse effects. A comparison of the available data on non-AhR-mediated neurotoxicity [18] and dioxin-like effects in wildlife indicated that the dioxin-like effects are more sensitive endpoints (Giesy and Kannan 1998). Although encouraging, the comparison is provisional because the neurotoxic effects are not as well studied as dioxin-like effects, non-dioxin-like effects include endpoints other than neural effects, and some endpoints may be affected through both AhR-mediated and non-dioxin-like pathways. For example, thyroid function may be affected by both pathways. In one study, the relative potency of different extracts in depressing serum levels of thyroxine (the main thyroid hormone) in rats was not well predicted by TEQ. An air extract proportionally enriched in lower chlorinated congeners and depleted in higher chlorinated congeners, dioxins, and dibenzofurans, exhibited more severe effects on thyroxine levels at the same TEQ concentrations as soil or dust extracts with the converse congener compositions (Figure 2A in Li and Hansen 1996). Although in most situations, TEQ-based assessments show good correlations with toxic effects and appear to provide an adequate margin of safety for non-dioxin-like effects as well, the potential for non-dioxin-like processes remains an uncertainty until our understanding of non-AhR-mediated processes improves.

> "The spectrum of activity produced by [non-coplanar] congeners has not been fully explored, and the mechanisms by which their known actions are produced are emerging but remain to be fully elucidated. The toxicodynamic interactions between non-coplanar PCBs and the actions produced by coplanar PCBs which bind to the Ah-receptor remain to be investigated. Similarly, the actions and interactions of hydroxylated and other metabolites of PCBs remain to be studied in sufficient depth. At the present time, it is clear that non-coplanar PCBs alter signal transduction pathways and interrupt intracellular Ca^{2+} homeostasis. A common site of action responsible for all of the actions of non-coplanar PCBs, analogous to the Ah-receptor utilized by coplanar PCBs, has not been found ..." (Fisher, et al. 1998).

In summary, the two major approaches for PCB risk assessment have converse strengths and uncertainties. For Aroclor-based approaches, uncertainties are low for interactions between congeners and multiple toxic mechanisms, but uncertainties increase as the congener composition of environmental samples is altered from the original Aroclor composition by weathering or bioaccumulation. The Aroclor approach does not readily allow for assessment of combined risk of PCBs and other chemicals with dioxin-like toxicity. For the currently available TEQ-based approaches, results are not affected by weathering, but uncertainties are associated with TEF values and additivity assumptions for calculated TEQs, interspecific differences in cellular responses and *in*

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[18] The situation is complicated by possible neurotoxicity caused by dioxin-like congeners as well as non-dioxin-like congeners.

vitro to *in vivo* extrapolations for bioassay TEQs, and an inability to account for non-dioxin-like effects. The TEQ approaches facilitate assessment of combined risk of PCBs and other chemicals with dioxin-like toxicity, although uncertainty remains for calculated TEQs by the limited number of consensus TEFs (risks may be underestimated due to dioxin-like chemicals without TEFs), and for bioassay TEQs by toxicokinetic considerations (risks may be overestimated by cellular responses to chemicals that would not cause toxicity in intact animals).

6.2.2 Interspecific Extrapolation and Laboratory-to-Field Extrapolation

Extrapolation of toxicity data from tested species to wildlife is another source of uncertainty in TRVs that includes two categories–extrapolations between different species, and extrapolations from laboratory conditions (captivity) to field conditions.[19] There is no interspecific extrapolation for mink because the TRVs are based on studies of captive mink, but the difference between conditions in captivity and in the wild is a source of uncertainty. Both categories of uncertainty pertain to the bird TRVs, which are based on studies of captive chicken.

Captive animals are well fed, do not have to compete for resources, are less active, usually protected from weather extremes, and in general are subject to less stress compared to wild animals.[20] The toxicity of a tested chemical is often greater in stressed animals, for example, in a review of fish toxicity, nutritional status altered the relative toxicity between laboratory and field situations by as much as 10-fold, and temperature stress by as much as 100-fold (Heugens, et al. 2001). Stressor interactions are often nonlinear, complicating their assessment (Power 1997), and may involve complex interactions. The adverse effects of PCBs on stress responses were increased by poor nutritional status (Quabius, et al. 2000), which implies that a synergistic interaction of PCB exposure and nutritional stress could decrease the capability to respond to additional stressors. Kammenga, et al. (2001) discuss examples in which exposure to toxic substances increases sensitivity to other environmental variables such that the exposed population becomes more vulnerable to changes in these other variables than to the direct toxicant effects. Another difference between captive and wild animals is that wild animals are exposed to a wider variety of toxic chemicals. In addition to interactions between stresses due to chemicals with different toxicological actions, wild animals may be exposed to chemicals that act though the same toxicological mechanisms as the chemical of concern, thereby increasing the toxicity of a given level of exposure compared to captive animals with controlled exposures. Other endpoints might be more sensitive or result in greater overall impact in the field compared to the endpoints studied under controlled conditions (Section 6.1.6). Related to this, laboratory studies are usually not performed over an entire life cycle, and effects in the field may differ from those in laboratory studies because of cumulative effects, greater sensitivity at other developmental or life stages than the ones investigated, or interactions between generations (for example, impaired parental care).

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[19] Another source of uncertainty for risk assessment involves the exposure assumptions. This is not addressed here because it does not affect the TRV values. For example, risk in the field may differ from modeled risk because the wildlife are feeding on a different mix of food items or in other locations than assumed in the model that results in differences between field and modeled exposures. However, exposure uncertainty concerns whether the TRVs have been or are likely to be exceeded, not the particular values of the TRVs.

[20] This may not hold for species that can not tolerate captivity, that is, the stress of being confined may outweigh the reduced stress of being cared for, but species intolerant of captivity can not be used for toxicity testing.

An example of greater adverse effects in a field study than expected from laboratory studies on related species is the high sensitivity of wood ducks to egg TEQ concentrations in the field–significant reductions in hatchability and live duckling production occurred at egg TEQs of 20-50 ppt (White and Seginak 1994; White and Hoffman 1995), which are comparable to the sensitivity of chicken–onset of embryonic mortality and deformities at 10-20 ppt dioxin egg concentration (Verrett 1976 as cited in Hoffman, et al. 1996), and LD_{50} (lethal dose to 50 % of embryos) of 122-297 ppt (Henshel, et al. 1997). This outcome would not be expected on the basis of laboratory studies with other ducks, which show much less sensitivity to PCBs compared to chicken–LD_{50} of 3-40 ppb congener 77 (one of the dioxin-like congeners) in chicken eggs, but no effects in mallard or goldeneye duck eggs at 5000 ppb congener 77 (various studies, see Table 3 in Hoffman, et al. 1996); and reduced hatchability at less than 1 ppm A1242 in chicken eggs, but no effects on hatchability at 105 ppm A1242 in mallard eggs (various studies, see Table 2 in Hoffman, et al. 1996). Based on these laboratory comparisons, ducks are at least 100 times less sensitive than chicken to PCBs and dioxin-like effects. The unexpected sensitivity of wood ducks in the field may have occurred because of differences among duck species (wood duck may be orders of magnitude more sensitive than mallard or goldeneye), unmeasured co-contaminant exposure contributing to toxicity in the field, stressor interactions not present in captivity, or exposure duration effects. Another example involves adverse effects on terns in the Great Lakes (see discussion in Hoffman, et al. 1998).

The sensitivity of different bird species to PCBs spans several orders of magnitude, and chicken are the most sensitive of the species tested to date (Bosveld and Van den Berg 1994; Barron, et al. 1995; Eisler and Belisle 1996; Hoffman, et al. 1996 and 1998). Use of chicken-based TRVs is inappropriate when species-specific toxicity data are available, and is generally considered inappropriate when data are available for closely related species (although the available toxicity data for ducks poorly predicted field effects for wood duck). The chicken-based PCB TRVs are recommended as a conservative estimator of risk for birds of unknown sensitivity to PCBs. Since chicken are more sensitive than other bird species tested so far, the likelihood of chicken TRVs under predicting risk for other species of unknown sensitivity is probably low, therefore use of uncertainty factors for interspecific extrapolation is not recommended. Although the same rationale indicates that chicken data for PCB toxicity is likely to overestimate risks to PCBs for other bird species, the wood duck example shows that this is not certain–the margin between laboratory effect levels in chicken and field effect levels in other species may be unexpectedly small. Also, PCB or dioxin toxicity has been studied in a relatively small number of bird species under controlled conditions. While the extremes of sensitivity are known to widely diverge, the overall distribution of species sensitivities within this range is poorly known.

The degree of conservatism of applying unmodified chicken-based PCB TRVs to species of unknown sensitivity can be evaluated by comparison to the bird PCB TRV used in the Great Lakes Initiative (GLI) for deriving water quality criteria for the protection of wildlife (USEPA 1995a). The GLI PCB TRV for birds is based on a LOAEL of 1.8 mg/kg_{BW}-d in pheasant (Dahlgren, et al. 1972), which was divided by an interspecific extrapolation uncertainty factor of 3 and a LOAEL to NOAEL uncertainty factor of 3. Therefore the calculated LOAEL for species of unknown sensitivity was 0.6 mg/kg_{BW}-d and the NOAEL 0.2 mg/kg_{BW}-d (only the NOAEL was used for deriving the water quality criteria). These values bracket the recommended TRVs of 0.4 to 0.5 mg/kg_{BW}-d based on chicken PCB TRVs without uncertainty factors. This comparison demonstrates that the conservatism of chicken-based PCB TRVs is consistent with that of previous agency practice for determining environmental PCB limits for protection of wildlife.

In summary, the bird TRVs proposed in this effort provide an appropriate level of conservatism for estimating risk to species of unknown sensitivity to PCBs. The TRVs are unlikely to underestimate risk. By design, they are more likely to overestimate risk, which is a necessary bias for accounting for the uncertainty regarding the sensitivity of untested species. Although interspecific differences in PCB sensitivity span several orders of magnitude, indicating potentially large uncertainty in assessing risk to untested species, the degree of conservatism associated with the TRVs in the present effort is consistent with prior agency practice.

There is no interspecific extrapolation for the mink TRVs, but uncertainty is associated with laboratory to field extrapolation. The uncertainty of laboratory to field extrapolations is that potential effects are more likely to be underestimated, rather than overestimated, for the various reasons discussed above. For Aroclor-based risk estimates in particular, a common observation is that toxicity is underestimated. This may be due to preferential biomagnification of toxic congeners that increase toxicity compared to the source Aroclor; exposure to other contaminants that either act through the same toxicological mechanisms as PCBs, thereby decreasing the amount of PCB exposure that can be tolerated without adverse effects, or acting as separate but additional stressors; or other non-chemical stressor interactions. These sources of uncertainty are addressed by the recommendation to use the lower of the derived TRVs.

As discussed in Section 6.1.5, the recommended mink TRVs are reasonably consistent with the value used by the GLI for calculating water quality criteria for protection of wildlife.

7. Conclusions

This effort demonstrates that toxicity reference values (TRVs) can be successfully derived through evaluation of dose-response plots in which data are aggregated from multiple studies by normalizing the treatment responses by the respective control responses of each study. The combined data sets better define the shape of dose-response relationship by increasing the number of doses plotted, thereby providing more information for decision-making compared to statistically-defined no or lowest observed adverse effect levels (NOAELs or LOAELs), which are influenced by multiple factors unrelated to toxicity and do not provide dose-response information. Although uncertainties may be introduced by differences in the experimental protocols of the various studies that are combined, such as differences in exposure duration or route, significant effects are readily apparent as inconsistencies in the dose-response plots.

The results of this exercise show that dose-response plots are not highly sensitive to moderate differences in exposure duration. The few differences in exposure route among the aggregated studies also did not result in obvious distortions of dose-response relationships (contaminated food vs. contaminated water, or egg injection vs. maternal transfer to eggs). In the cases in which dose-response inconsistencies are apparent between study results, the data can be stratified (considered separately) for analysis if multiple patterns are evident, or that endpoint can be dropped from further consideration if the data exhibit no interpretable pattern. In other words, the dose-response plots provide their own safeguard against utilization of incompatible data by exhibiting divergent patterns or uninterpretable relationships inconsistent with known toxicological models.

The dose-response plots exhibit very steep transitions between PCB exposures causing no adverse effects and those resulting in severe adversity–mostly less than 2- or 3-fold gradients in dose or dietary concentration

between the response extremes. This has two implications: 1) small exceedances of PCB TRVs are likely to result in severe effects on reproductive success, and 2) the calculated PCB TRVs are relatively insensitive to the choice of effect size (the percent decrease in response that is of concern for risk management) because the range of values over which the TRVs can vary is narrow.

Two significant observations can be made from the dose-response plots for mink (actually dietary concentration-response plots). 1) PCBs exhibit a hormetic effect (enhanced reproductive performance) at doses lower than the threshold for adverse effects for the number of live kits produced per mated female in feeding trials performed with either commercial PCB products or field-contaminated prey. 2) In both commercial PCB product (Clophen A50) and field-contaminated prey studies with mink, the exposure-response relationships differ between studies performed over a single breeding season versus those in which exposures are continued over 2 breeding seasons or 2 generations of female mink. Continuous PCB exposure over 2 breeding seasons or 2 generations of female mink results in more severe adverse effects on live kit production, kit survival, and, to a lesser extent, kit bodyweight, in comparison to the effects of exposure over a single breeding season. The mean difference in low effect TRVs for the various endpoints in the two studies is a 50 % decrease associated with 2-breeding season or generation exposures as compared to single-breeding season exposure. This has obvious implications for long-term sustainability of mink at contaminated sites. Since 2-breeding season or generation studies have not been performed with Aroclors, the mink Aroclor TRVs are adjusted by the mean response decrement observed in the Clophen and field-contaminated studies to ensure long-term sustainability.

TRVs based on controlled exposures to Aroclors are given in Table 1 (Section 1). The lower of the TRVs are recommended to account for increases in toxicity PCBs in the field compared to that of Aroclors under controlled conditions, which may be related to changes in source congener composition by weathering and bioaccumulation, concurrent exposure to other contaminants acting through the same toxicological mechanisms as PCBs (thereby reducing the tolerable exposure to PCBs), or interactions with other stressors (chemical, physical, or biological) not present in captivity. Uncertainty factors are not recommended for interspecific extrapolation because the TRVs are based on data for sensitive species.

Although the TRVs are conservatively derived (chicken are sensitive to PCBs, and mink values are adjusted for long-term exposures), the recommended values and level of conservatism are consistent with prior agency practice. Both the bird and mink TRVs are bracketed by the NOAEL and LOAEL values used in the development of PCB water quality criteria for the protection of wildlife by the Great Lakes Initiative. As such, the recommended TRVs represent a refinement of the toxicity information used for the GLI, and share a similar degree of conservatism in their application.

8. Literature Cited

Aarts, J., M. Denison, M. Cox, M. Schalk, P. Garrison, K. Tullis, L. de Haan, and A. Brouwer. 1995. Species-specific antagonism of Ah receptor action by 2,2',3,3',4,4'-hexachlorobiphenyl. Eur J Pharmacol Environ Toxicol Pharmacol 293: 463-474.

Aulerich, R. and R. Ringer. 1977. Current status of PCB toxicity to mink, and effect on their reproduction. Arch Environ Contam Toxicol 6: 279-292.

Bachour, C., K. Failing, S. Georgii, I. Elmadfa, and H. Brunn. 1998. Species and organ dependence of PCB contamination in fish, foxes, roe deer, and humans. Arch Environ Contam Toxicol 35: 666-673.

Barron, M., H. Galbrith and D. Beltman. 1995. Comparative reproductive and developmental toxicology of PCBs in birds. Comp Biochem Physiol 112C(1): 1-14.

Birnbaum, L. 1999. TEFs: a practical approach to a real-world problem. Human Ecol Risk Assessm 5: 13-24.

Bleavins, M., R. Aulerich, and R. Ringer. 1980. Polychlorinated biphenyls (Aroclors 1016 and 1242): Effects on survival and reproduction in mink and ferrets. Arch Environ Contam Toxicol 9: 627-635.

Bosveld, A. and M. Van den Berg. 1994. Effects of polychlorinated biphenyls, dibenzo-*p*-dioxins, and dibenzofurans on fish-eating birds. Environ Rev 2: 147-166.

Briggs, D. and J. Harris. 1972. Polychlorinated biphenyls influence on hatchability. Poultry Sci 52: 1291-1294.

Britton, W. and T. Huston. 1973. Influence of polychlorinated biphenyls in the laying hen. Poultry Sci 52: 1620-1624.

Brunström, B., B. Lund, A. Bergman, L. Asplund, I. Athanassiadis, M. Athanasiadou, S. Jensen, and J. Örberg. 2001. Reproductive toxicity in mink (*Mustela vison*) chronically exposed to environmentally relevant polychlorinated biphenyl concentrations. Environ Toxicol Chem 20: 2318-2327.

Cecil, H., J. Bitman, R. Lillie, G. Fries, and J. Verrett. 1974. Embryotoxic and teratogenic effects in unhatched fertile eggs from hens fed polychlorinated biphenyls (PCBs). Bull Environ Contam Toxicol 11: 489-495.

Chapman, G., D. Denton, and J. Lazorchak. 1995. Short-term Methods for Estimating the Chronic Toxicity of Effluents and Receiving Waters to West Coast Marine and Estuarine Organisms, 1st ed. Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati. EPA/600/R-95-136.

Chapman, J. and G. Feldhamer (eds.). 1982. Wild Mammals of North America: Biology, Management, and Economics. John Hopkins Univ. Press, Baltimore. 1147 p.

Chapman, P. 1998. Alternatives to the NOEC based on regression analysis. Annex 7 in Report of the OECD Workshop on Statistical Analysis of Aquatic Toxicity Data. Environment Directorate, Organization for Economic Co-operation and Development. OECD Environmental Health and Safety Publications, Series on Testing and Assessment No. 10. ENV/MC/CHEM (98)18.

Clemons, J., D. Dixon, and N. Bols. 1997. Derivation of 2,3,7,8-TCDD equivalent factors (TEFs) for selected dioxins, furans, and PCBs with rainbow trout and rat liver cell lines and the influence of exposure time. Chemosphere 34: 1105-1119.

Cooch, E., R. Rockwell, S. Brault. 2001. Retrospective analysis of demographic responses to environmental change: a lesser snow goose example. Ecol Monog 71: 377-400.

Crane, M. and M. Newman. 2000. What level of effect is a no observed effect? Environ Toxicol Chem 19: 516-519.

Crump, K. 1984. A new method for determining allowable daily intakes. Fund Appl Toxicol 4: 854-871.

Dahlgren, R., R. Linder, and C. Carlson. 1972. Polychlorinated biphenyls: Their effects on penned pheasants. Environ Health Perspect. Experimental Issue 1: 89-101.

DeVito, M. and L. Birnbaum. 1995. The importance of pharmacokinetics in determining the relative potency of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and 2,3,7,8-tetrachlorodibenzofuran. Fund Appl Toxicol 24: 145-148.

Dyke, P. and J. Stratford. 2002. Changes to the TEF schemes can have significant impacts on regulation and management of PCDD/F and PCB. Chemosphere 47: 103-116.

Eisler, R. and A. Belisle. 1996. Planar PCB Hazards to Fish, Wildlife, and Invertebrates: A Synoptic Review. National Biological Services Biological Report 31. 75 p.

Fischer, L., R. Seegal, P. Ganey, I. Pessah and P. Kodavanti. 1998. Symposium overview: toxicity of non-coplanar PCBs. Toxicol Sci 41:49-61.

Forbes, V., R. Sibly, and P. Calow. 2001. Toxicant impacts on density-limited populations: a critical review of theory, practice, and results. Ecol Appl 11: 1249-1257.

Ganey, P., J. Quensen, M. Mousa, S. Boyd, M. Wagner, and L. Fisher. 2000. Biological activity associated with noncoplanar polychlorinated biphenyls after microbial dechlorination of Aroclor 1242® and Aroclor 1254®. Environ Toxicol Chem 19: 1311-1316.

Giesy, J., D. Jude, D. Tillitt, R. Gale, J. Meadows, J. Zajieck, P. Peterman, D. Verbrugge, J. Sanderson, T. Schwartz, and M. Tuchman. 1997. Polychlorinated dibenzo-*p*-dioxins, dibenzofurans, biphenyls and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin equivalents in fish from Saginaw Bay, Michigan. Environ Toxicol Chem 16: 713-724.

Geisy, J. and Kannan, K. 1998. Dioxin-like and non-dioxin-like toxic effects of polychlorinated biphenyls (PCBs): Implications for risk assessment. Crit Rev Toxicol 28:511-569.

Gould, J., K. Cooper, C. Scanes. 1997. Effects of polychlorinated biphenyl mixtures and three specific congeners on growth and circulating growth-related hormones. Gen Compar Endrocrinol 106: 221-230.

Guruge, K. and S. Tanabe. 1997. Congener specific accumulation and toxic assessment of polychlorinated biphenyls in common cormorants, *Phalacrocorax carbo*, from Lake Biwa, Japan. Environ Pollut 96: 425-433.

Halbrook, R., R. Aulerich, S. Bursian, and L. Lewis. 1999. Ecological risk assessment in a large river-reservoir: 8. Experimental study of the effects of polychlorinated biphenyls on reproductive success in mink. Environ Toxicol Chem 18: 649-654.

Heaton, S., S. Bursian, J. Giesy, D. Tillitt, J. Render, P. Jones, D. Verbrugge, T. Kubiak and R. Aulerich. 1995a. Dietary exposure of mink to carp from Saginaw Bay, Michigan. 1. Effects on reproduction and survival, and the potential risks to wild mink populations. Arch Eviron Contam Toxicol 28: 334-343.

Heaton, S., S. Bursian, J. Giesy, D. Tillitt, J. Render, P. Jones, D. Verbrugge, T. Kubiak and R. Aulerich. 1995b. Dietary exposure of mink to carp from Saginaw Bay, Michigan. 2.Hematology and liver pathology. Arch Eviron Contam Toxicol 29: 411-417.

Henshel, D., B. Hehn, R. Wagey, M. Vo and J. Steeves. 1997. The relative sensitivity of chicken embryos to yolk- or air-cell-injected 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Environ Toxicol Chem 16: 725-732.

Heugens, E., A. Hendriks, T. Dekker, N. van Straalen, and W. Admiraal. 2001. A review of the effects of multiple stressors on aquatic organisms and analysis of uncertainty factors for use in risk assessment. Crit Rev Toxicol 31: 247-284.

Hoffman, D., C. Rice and T. Kubiak. 1996. PCBs and dioxins in birds. *In* Environmental Contaminants in Wildlife, Interpreting Tissue Concentrations. (W. Beyer, G. Heinz and A. Redmon-Norwood, eds.). Lewis, Boca Raton. pp. 165-207.

Hoffman, D., M. Melancon, P. Klein, J. Eisemann and J. Spann. 1998. Comparative developmental toxicity of planar polychlorinated biphenyl congeners in chickens, American kestrels, and common terns. Environ Toxicol Chem 17: 747-757.

Hornshaw, T., R. Aulerich and H. Johnson. 1983. Feeding Great Lakes fish to mink: Effects on mink accumulation and elimination of PCBs by mink. J Toxicol Environ Health 11: 933-946.

Isnard, P., P. Flammarion, G. Roman, M. Babut, P. Bastien, S. Bintein, L. Esserméant, J. Férard, S. Gallotti-Schmitt, E. Saouter, M. Saroli, H. Thiébaud, R. Tomassone, and E. Vindimian. 2001. Statistical analysis of regulatory ecotoxicity tests. Chemosphere 45: 659-669.

Jensen, S. 1977. Effect of PCB and DDT on mink (*Mustela vision*) during the reproductive season. Ambio 6: 239.

Johansson, M., S. Nilsson and B.-O. Lund. 1998. Interactions between methylsulfonyl PCBs and the glucocorticoid receptor. Environ Health Perspect 106: 769-772.

Jones, P., G. Ankley, D. Best, R. Crawford, N. DeGalan, J. Giesy, T. Kubiak, J. Ludwig, J. Newsted, D. Tillitt, and D. Verebrugge. 1993. Biomagnification of bioassay derived 2,3,7,8-tetrachlorodibenzo-p-dioxin equivalents. Chemosphere 26: 1203-1212.

Käkelä, A., R. Käkelä, H. Hyvärinen, and J. Asikainen. 2002. Vitamins A_1 and A_2 in hepatic tissue and subcellular fractions in mink feeding on fish-based diets and exposed to Aroclor 1242. Environ Toxicol Chem 21: 397-403.

Kammenga, J., C. Van Gestel, and E. Hornung. 2001. Switching life-history sensitivities to stress in soil organisms. Ecol Appl 11: 226-238.

Kihiström, J., M. Olsson, S. Jensen, Å. Johansson, J. Ahlbom, and A. Bergman. 1992. Effect of PCB and different fractions of PCB on the reproduction of the mink (*Mustela vison*). Ambio 21: 563-601.

Klemm, D., G. Morrison, T. Norberg-King, W. Peltier, and M. Heber. 1994. Short-term Methods for Estimating the Chronic Toxicity of Effluents and Receiving Waters to Marine and Estuarine Organisms, 2nd ed. Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati. EPA/600/4-91/003.

Koslowski, S., C. Metcalfe, R. Lazar, and G. Haffner. 1994. The distribution of 42 PCBs, including three coplanar congeners, in the food web of the western basin of Lake Erie. J Great Lakes Res 20: 260-270.

Leonards, P., T. de Vries, W. Minnaard, S. Stuijfzand, P. de Voogt, W. Cofino, N. van Straalen and B. van Hattum. 1995. Assessment of experimental data on PCB-induced reproduction inhibition in mink, based on an isomer- and congener-specific approach using 2,3,7,8-tetrachlorodibenzo-*p*-dioxin toxic equivalency. Environ Toxicol Chem 14: 639-652.

Leonards, P., Y. Zierikzee, U. Brinkman, W. Cofino, N. van Straalen, and B. van Hattum. 1997. The selective dietary accumulation of planar polychlorinated biphenyls in the otter (*Lutra lutra*). Environ Toxicol Chem 16: 1807-1815.

Lester, N., W. Dunlop, and C. Willox. 1996. Detecting changes in the nearshore fish community. Can J Fish Aquat Sci 53 (Supplement 1): 391-402.

Li, M.-H. and L. Hansen. 1996. Enzyme induction and acute endrocrine effects in prepubertal female rats receiving environmental PCB/PCDF/PCDD mixtures. Environ Health Perspect 104: 712-722.

Lillie, R., H. Cecil, J. Bitman, and G. Fries. 1974. Differences in response of caged white leghorn layers to various polychlorinated biphenyls (PCBs) in the diet. Poultry Sci 53: 726-732.

Lillie, R., H. Cecil, J. Bitman, G. Fries, and J. Verrett. 1975. Toxicity of certain polychlorinated and polybrominated biphenyls on reproductive efficiency of caged chickens. Poultry Sci 54: 1550-1555.

Lu, C., R. Baggs, D. Redmond, E. Henry, A. Schecter, and T. Gasiewicz. 1986. Toxicity and evidence for metabolic alterations in 2,3,7,8-tetrachlorodibenzo-*p*-dioxin-treated guinea pigs fed by total parental nutrition. Toxicol Appl Pharmacol 84: 439-453.

Ludwig, J., H. Kurita-Matsuba, H. Auman, M. Ludwig, C. Summer, J. Giesy, D. Tillitt, and P. Jones. 1996. Deformities, PCBs, and TCDD-equivalents in double-crested cormorants (*Phalacrorax auritus*) and Caspian Terns (*Hydroprogne caspia*) of the upper Great Lakes 1986-1991: testing a cause-effect hypothesis. J Great Lakes Res 22: 172-197.

Medway, W. and M. Kare. 1959. Water metabolism of the growing domestic fowl with special reference to water balance. Poultry Sci 38: 631-637.

Merritt, J. 1987. Guide to the Mammals of Pennsylvania. Univ. Pittsburg Press, Pittsburg. 408 p.

Metcalfe, T. and C. Metcalfe. 1997. The trophodynamics of PCBs, including mono- and non-ortho congeners, in the food web of north-central Lake Ontario. Sci Total Environ 201: 245-272.

Moore, D. and P. Caux. 1997. Estimating low toxic effects. Environ Toxicol Chem 16: 794-801.

NRC. 1998. Improving Fish Stock Assessments. National Research Council. National Academy Press, Washington. 177 p.

OECD. 1998. Report of the OECD Workshop on Statistical Analysis of Aquatic Toxicity Data. Environment Directorate, Organization for Economic Co-operation and Development. OECD Environmental Health and Safety Publications, Series on Testing and Assessment No. 10. ENV/MC/CHEM (98)18.

Platonow, N. and L. Karstad. 1973. Dietary effects of polychlorinated biphenyls on mink. Can J Comp Med 37: 391-400.

Platonow, N. and B. Reinhart. 1973. The effects of polychlorinated biphenyls Aroclor 1254 on chicken egg production fertility and hatchability. Can J Comp Med 37: 341-346.

Power, M. 1997. Assessing the effects of environmental stressors on fish populations. Aquat Toxicol 39: 151-169.

Quabius, E., D. Nolan, and S. Bonga. 2000. Influence of dietary exposure to polychlorinated biphenyl 126 and nutritional state on stress response in tilapia (*Oreochromis mossambicus*) and rainbow trout (*Onorhynchus mykiss*). Environ Toxicol Chem 19: 2829-2899.

Restum, J., S. Bursian, J. Giesy, J. Render, W. Helferich, E. Shipp, D. Verbrugge, and R. Aulerich. 1998. Multigenerational study of the effects of consumption of PCB-contaminated carp from Saginaw Bay, Lake Huron, on mink: 1. Effects on mink reproduction, kit growth, and survival, and selected biological parameters. J Toxicol Environ Health Part A 54: 343-375.

Rose, K. 2000. Why are quantitative relationships between environmental quality and fish populations so elusive? Ecol Appl 10: 367-385.

Safe, S. 1998. Hazard and risk assessment of chemical mixtures using the toxic equivalency factor approach. Environ Health Perspect 106 (Supplement 4): 1051-1058.

Scholze, M., W. Boedeker, M. Faust, T. Backhaus, R. Altenburger, and L. Grimme. 2001. A general best-fit method for concentration-response curves and the estimation of low-effect concentrations. Environ Toxicol Chem 20: 448-457.

Schuur, A., A. Brouwer, Å. Bergman, M. Coughtrie, and T. Visser. 1998. Inhibition of thyroid hormone sulfation by hydroxylated metabolites of polychlorinated biphenyls. Chemico-Biol Interact 109: 293-297.

Scott, M. 1977. Effects of PCBs, DDT and mercury compounds in chickens and Japanese quail. Fed Proceed 36: 1888-1893.

Seefeld, M., S. Corbett, R. Keesey, and R. Peterson. 1984. Characterization of the wasting syndrome in rats treated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Toxicol Appl Pharmacol 73: 311-322.

Shea, K. and M. Mangel. 2001. Detection of population trends in threatened coho salmon (*Oncorhynchus kisutch*). Can J Fish Aquat Sci 58: 375-385.

Shipp, E., J. Restum, J. Giesy, S. Bursian, R. Aulerich, and W. Helferich. 1998. Multigenerational study of the effects of consumption of PCB-contaminated carp from Saginaw Bay, Lake Huron, on mink. 2. Liver PCB concentration and induction of hepatic cytochrome P-450 activity as a potential biomarker for PCB exposure. J Toxicol Environ Health Part A 54: 377-401.

Sotherland, P. and H. Rahn. 1987. On the composition of bird eggs. Condor 89: 48-65.

Summer, C., J. Giesy, S. Bursian, J. Render, T. Kubiak, P. Jones, D. Verbrugge, and R. Aulerich. 1996a. Effects induced by feeding organochlorine-contaminated carp from Saginaw Bay, Lake Huron, to laying white leghorn hens. I. Effects on health of adult hens, egg production, and fertility. J Toxicol Environ Health 49: 389-407.

Summer, C., J. Giesy, S. Bursian, J. Render, T. Kubiak, P. Jones, D. Verbrugge, and R. Aulerich. 1996b. Effects induced by feeding organochlorine-contaminated carp from Saginaw Bay, Lake Huron, to laying white leghorn hens. II. Embryotoxic and teratogenic effects. J Toxicol Environ Health 49: 409-438.

Suter, G. 1996. Abuse of hypothesis testing statistics in ecological risk assessment. Human Ecol Risk Assessm 2: 331-349.

Tanaka, Y. and J. Nakanishi. 2001. Model selection and parameterization of the concentration-response functions for population-level effects. Environ Toxicol Chem 20: 1857-1865.

Tillitt, D. 1999. The toxic equivalents approach for fish and wildlife. Human Ecol Risk Assessm 5: 25-32.

Tillitt, D., J. Giesy, and G. Ankley. 1991. Characterization of the H4IIE rat hepatoma cell bioassay as a tool for assessing toxic potency of planar halogenated hydrocarbons in environmental samples. Environ Sci Technol 25: 87-92.

Tillitt, D., G. Ankley, J. Giesy, J. Ludwig, H. Kurita-Matsuba, D. Weseloh, P. Ross, C. Bishop, L. Sileo, K. Stromborg, J. Larson, and T. Kubiak. 1992. Polychlorinated biphenyl residues and egg mortality in double-crested cormorants from the Great Lakes. Environ Toxicol Chem 11: 1281-1288.

Tillitt, D., R. Gale, J. Meadows, J. Zajicek, P. Peterman, S. Heaton, P. Jones, S. Bursian, T. Kubiak, J. Giesy, and R. Aulerich. 1996. Dietary exposure of mink to carp from Saginaw Bay. 3. Characterization of dietary exposure to planar halogenated hydrocarbons, dioxin equivalents, and biomagnification. Environ Sci Technol 30: 283-291.

Trowbridge, A. and D. Swackhamer. 2002. Preferential biomagnification of aryl hydrocarbon hydroxylase-inducing polychlorinated biphenyl congeners in the Lake Michigan, USA, lower food web. Environ Toxicol Chem 21: 334-341.

Tumasonis, C., B. Bush, and F. Baker. 1973. PCB levels in egg yolks associated with embryonic mortality and deformity of hatched chicks. Arch Environ Contam Toxicol 1: 312-324.

Tyre, A., H. Possingham, and D. Niejalke. 2001. Detecting environmental impacts on metapopulations of mound spring invertebrates, assessing an incidence function model. Environ Internat 27: 225-229.

USEPA. 1995a. Great Lakes Water Quality Initiative Criteria Documents for the Protection of Wildlife: DDT, Mercury, 2,3,7,8-TCDD, PCBs. Office of Water. EPA-820-B-95-008.

USEPA. 1995b. The Use of the Benchmark Dose Approach in Health Risk Analysis. Risk Assessment Forum. EPA/630/R-94/007.

USEPA. 1997. Ecological Risk Assessment Guidance for Superfund: Process for Designing and Conducting Ecological Risk Assessments, Interim Final. Environmental Response Team, Edison, NJ, EPA 540-R-97-006. www.epa.gov/superfund/programs/risk/ecorisk/ecorisk.htm

Van den Berg, M. and 23 co-authors. 1998. Toxic equivalency factors (TEFs) for PCBs, PCDFs, PCDFs for humans and wildlife. Environ Health Perspect 106: 775-792.

van Leeuwen, F. 1999. van Leeuwen's response [letter]. Environ Health Perspect 107: A493.

Verrett, M. 1976. Investigations of the toxic and teratogenic effects of halogenated dibenzo-*p*-dioxins and dibenzofurans in the developing chicken embryo. *In* Memorandum report. U.S. Food and Drug Administration, Washington, D.C.

White, D. and J. Seginak. 1994. Dioxins and furans linked to reproductive impairment in wood ducks. J Wildl Manage 58: 100-106.

White, D. and D. Hoffman. 1995. Effects of polychlorinated dibenzo-*p*-dioxins and dibenzofurans on nesting wood ducks (*Aix sponsa*) at Bayou Meto, Arkansas. Environ Health Perspect 103 (Suppl 4): 37-39.

Wren, C., D. Hunter, J. Leatherland, and P. Stokes. 1987. The effects of polychlorinated biphenyls and methylmercury, singly and in combination on mink. I. uptake and toxic responses. Arch Environ Contam Toxicol 16: 441-447; and II. reproduction and kit development. Arch Environ Contam Toxicol 16: 449-454.

Figure 1. Live Kits per Mated Female Mink Exposed to Commercial PCB Product for 1 Breeding Season

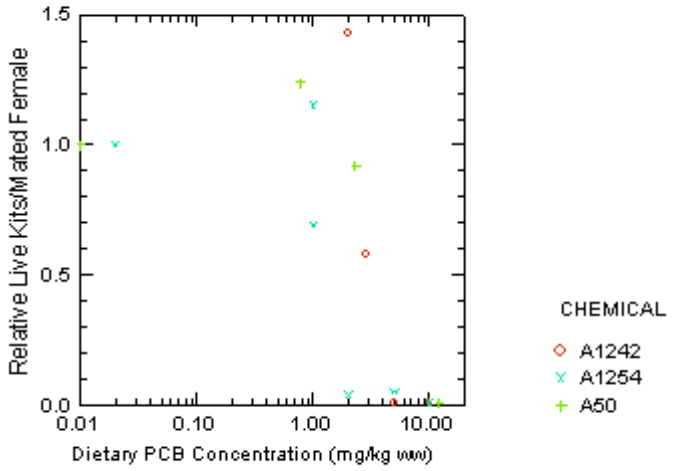
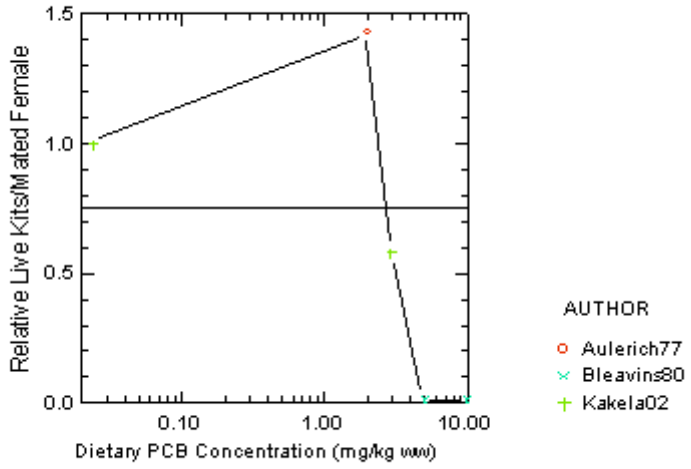


Figure 2. Live Kits per Mated Female Mink Exposed to Commercial Aroclor 1242 for 1 Breeding Season



Author is lead author and date. See notes to Table 3 for citations

Figure 3. Live Kits per Mated Female Mink Exposed to Commercial Aroclor 1254 for 1 Breeding Season

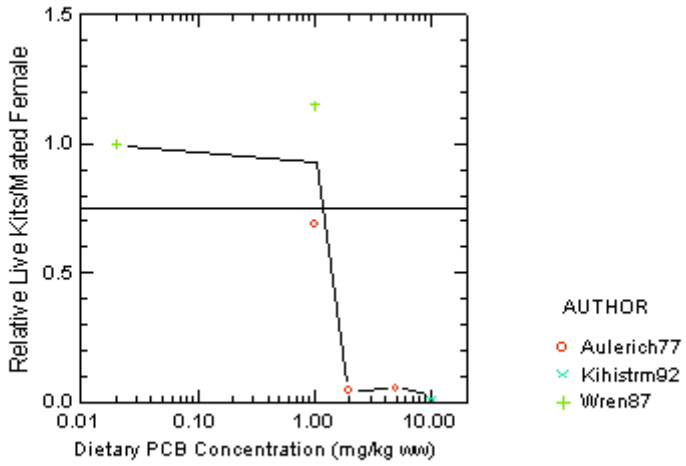


Figure 4. Mink Kit Bodyweight, Maternal Exposure to Commercial PCB Product for 1 Breeding Season

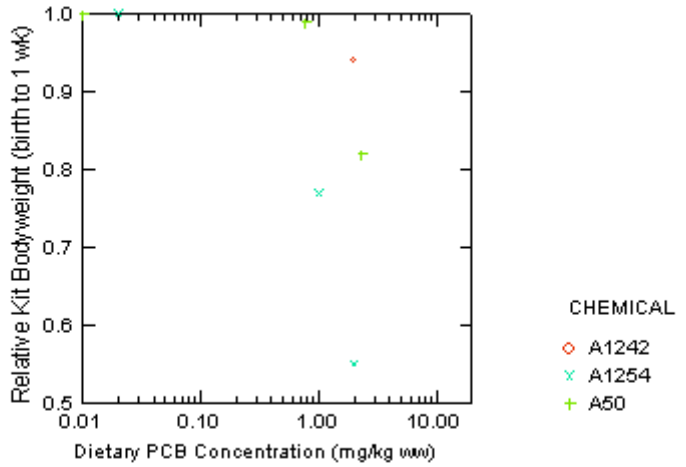


Figure 5. Mink Kit Bodyweight at Birth, Maternal Exposure to Commercial Aroclor 1254 for 1 Breeding Season

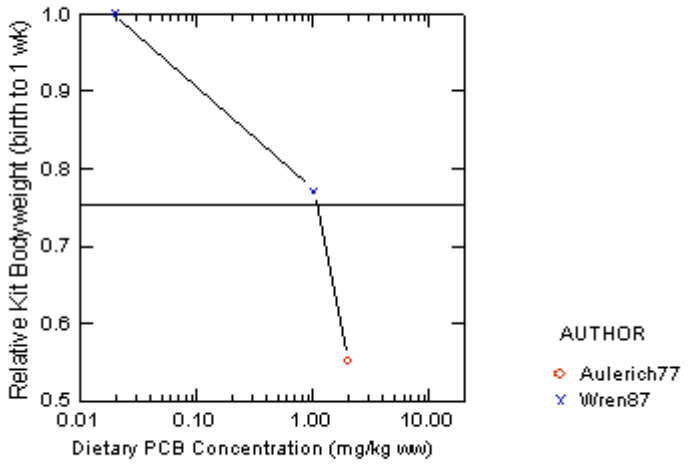


Figure 6. Mink Kit Survival, Maternal Exposure to Commercial Aroclor 1254 for 1 Breeding Season

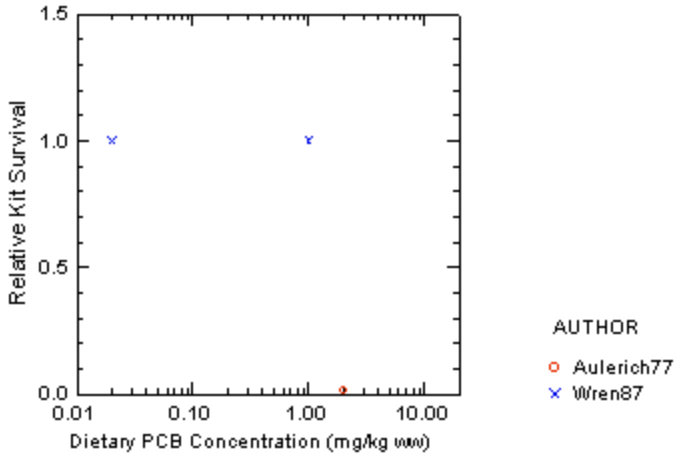


Figure 7. Live Kits per Mated Female Mink Exposed to Commercial Clophen A50 for Multiple Breeding Seasons (Brunström, et al. 2001; Kihlström, et al. 1992)

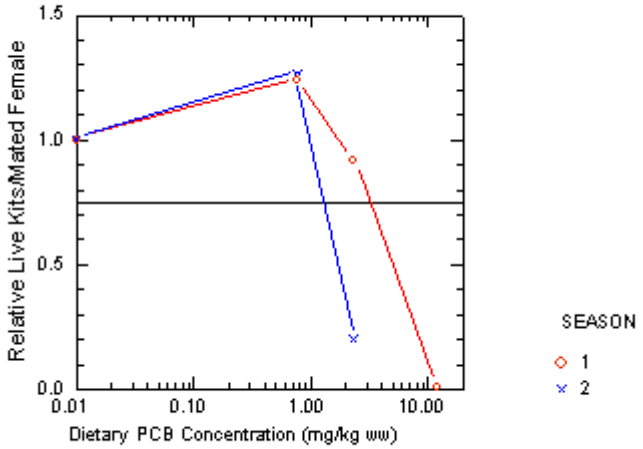


Figure 8. Live Kits per Mated Female Mink Exposed to Field-contaminated Fish for Multiple Breeding Seasons or Generations (Restum, et al. 1998)

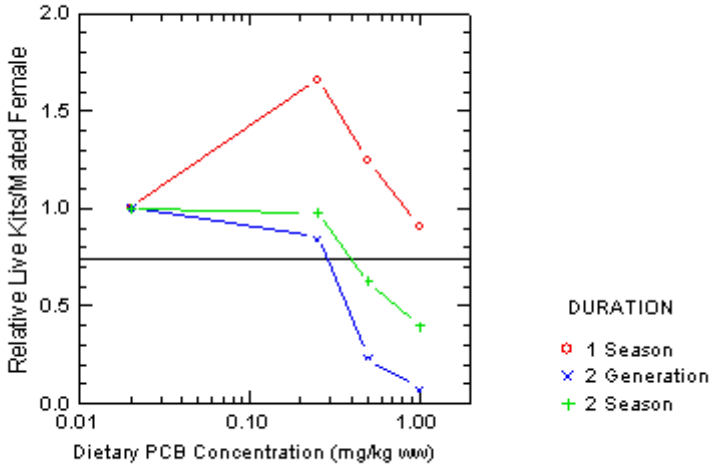


Figure 9. Mink Kit Bodyweight at Birth, Maternal Exposure to Commercial Clophen A50 for Multiple Breeding Seasons (Brunström, et al. 2001)

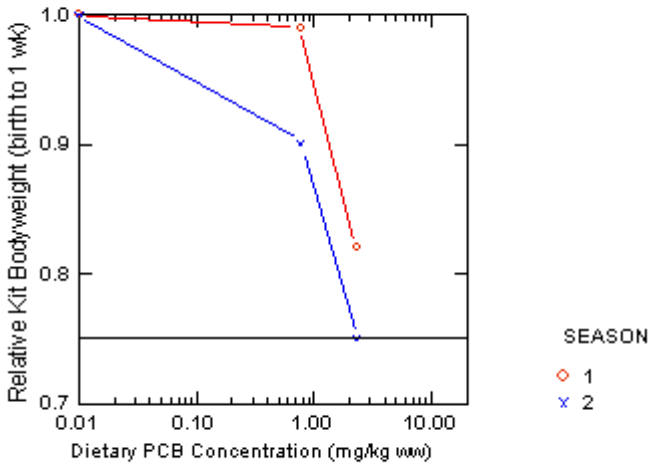


Figure 10. Mink Kit Bodyweight at Birth, Maternal Exposure to Field-contaminated Fish for Multiple Breeding Seasons or Generations (Restum, et al. 1998)

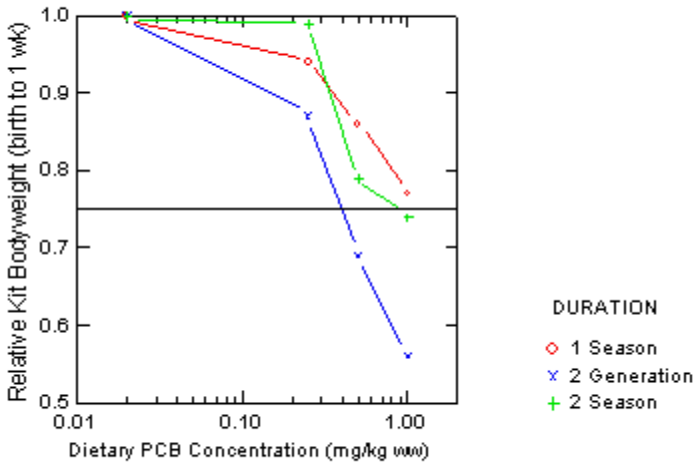


Figure 11. Mink Kit Survival, Maternal Exposure to Commercial Clophen A50 for 2 Breeding Seasons (Brunström, et al. 2001)

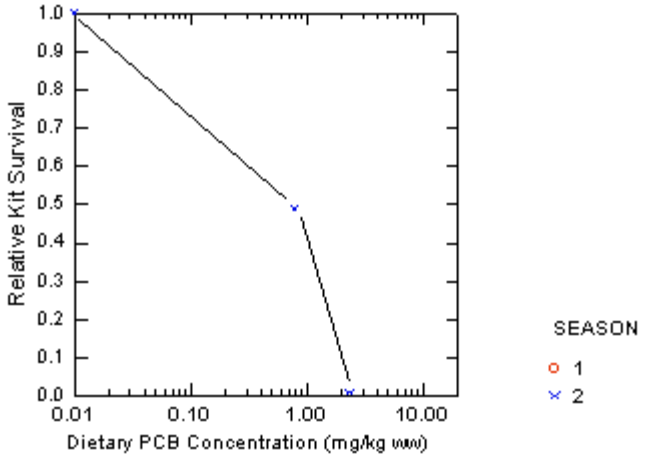


Figure 12. Mink Kit Survival, Maternal Exposure to Field-contaminated Fish for Multiple Breeding Seasons or Generations (Restum, et al. 1998)

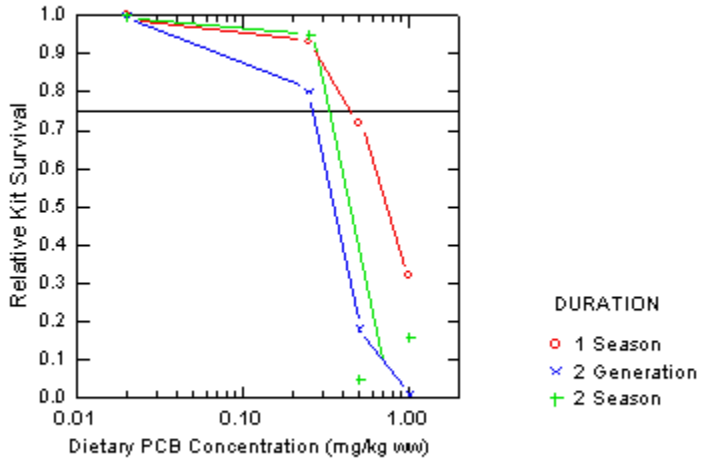


Figure 13. Live Kits per Mated Female Mink Exposed to Field-contaminated Prey for 1 Breeding Season

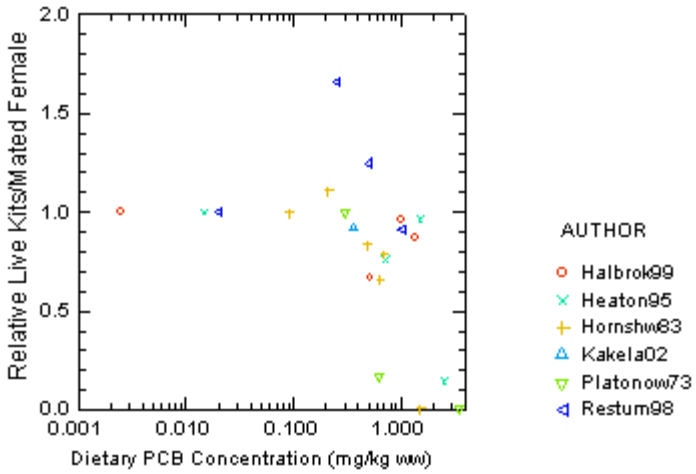


Figure 14. Mink Kit Bodyweight, Maternal Exposure to Field-contaminated Fish for 1 Breeding Season

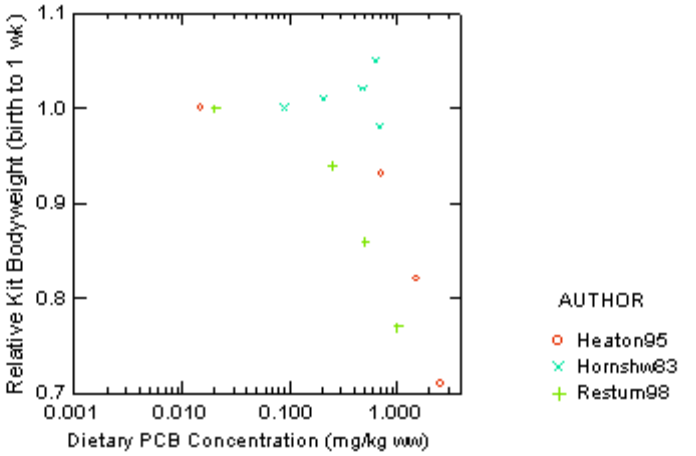


Figure 15. Mink Kit Survival, Maternal Exposure to Field-contaminated Prey for 1 Breeding Season

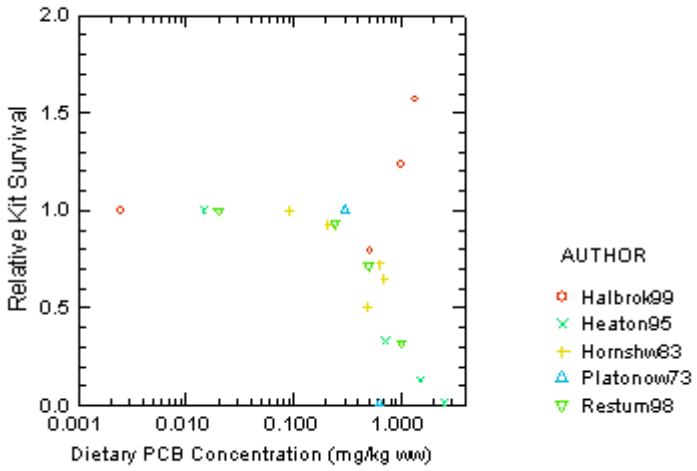


Figure 16. Comparison of Dose-response Relationships for Individual and Aggregated Studies of Hatchability vs. A1248 Dose to Hens

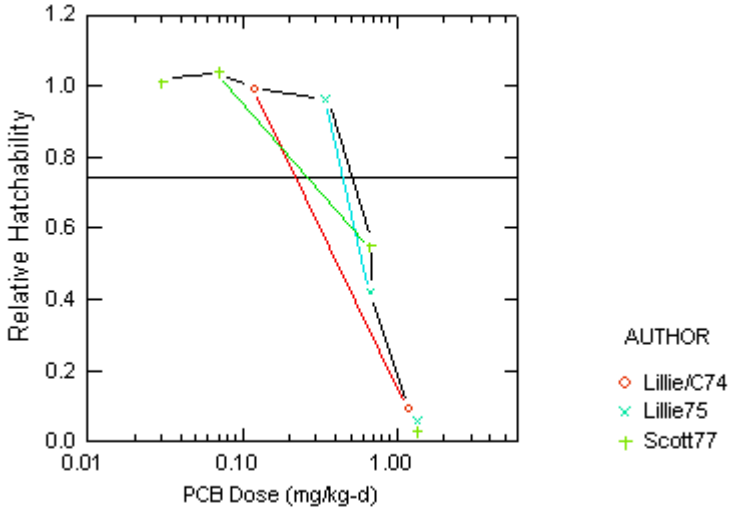


Figure 17. Hatchability, PCB Dose to Chicken Hens

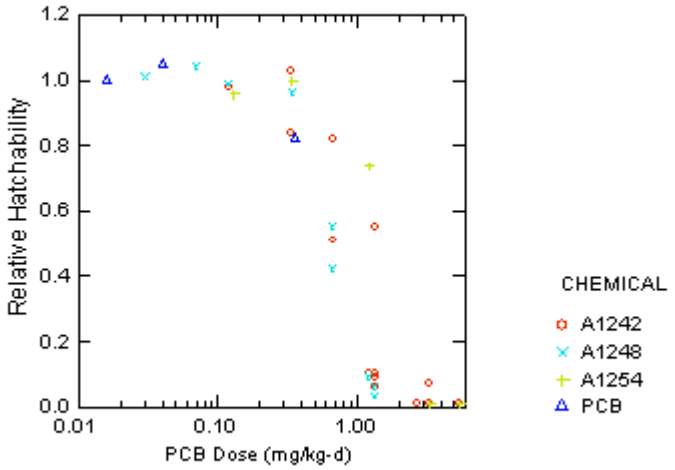
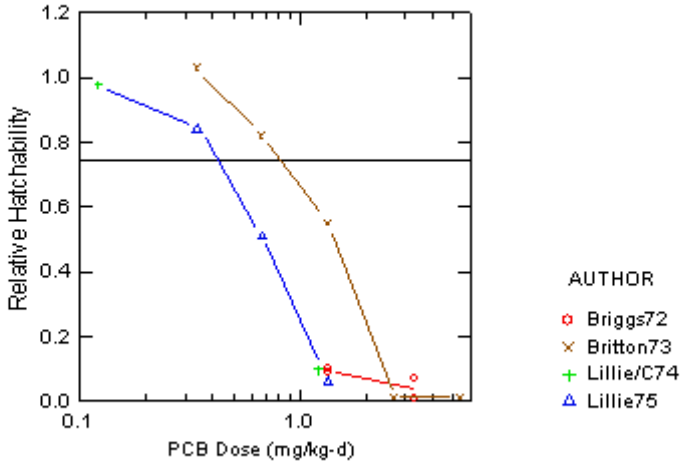


Figure 18. Hatchability, Aroclor1242 Dose to Chicken Hens



Author is lead author and date. See notes to Table 3 for citations.

Figure 19. Hatchability, Aroclor 1248 Dose to Chicken Hens

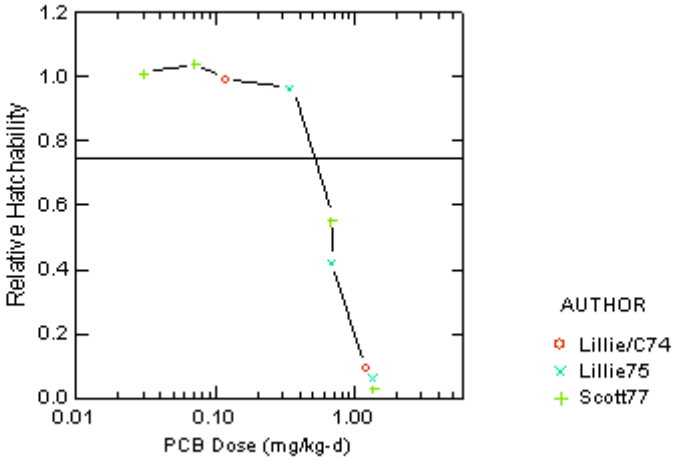


Figure 20. Hatchability, Aroclor 1254 Dose to Chicken Hens

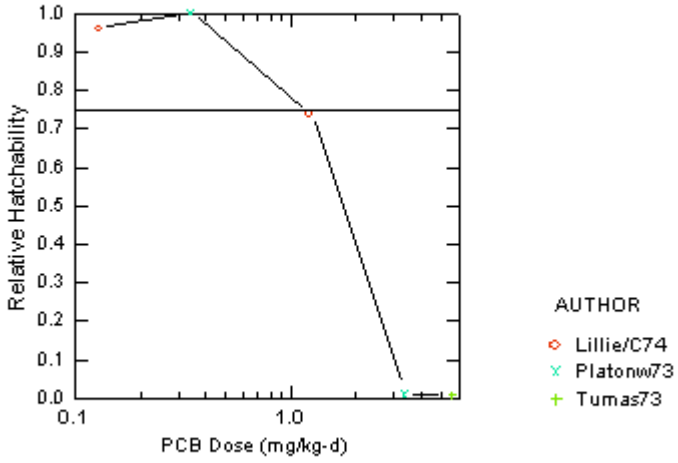


Figure 21. Hatchability, PCB Residues in Chicken Eggs

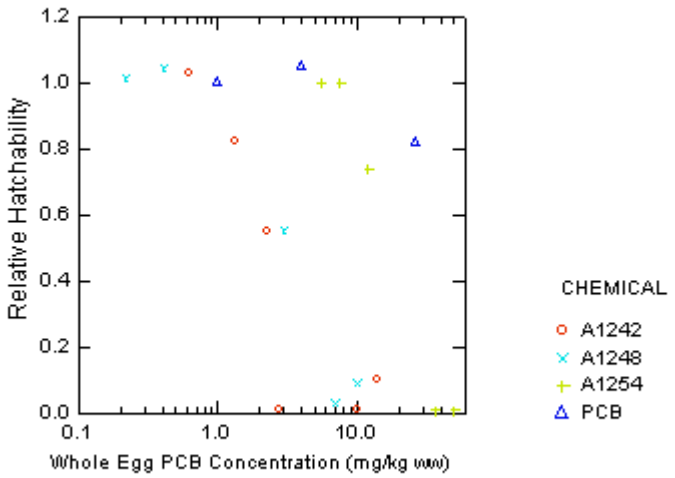


Figure 22. Hatchability, Aroclor 1242 Residues in Chicken Eggs

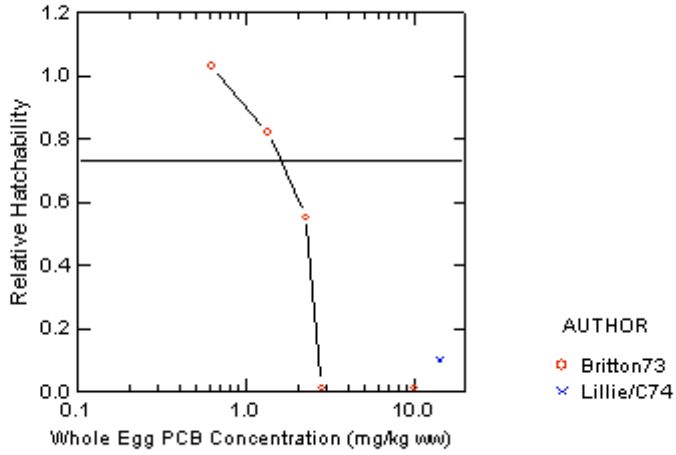


Figure 23. Hatchability, Aroclor 1248 Residues in Chicken Eggs

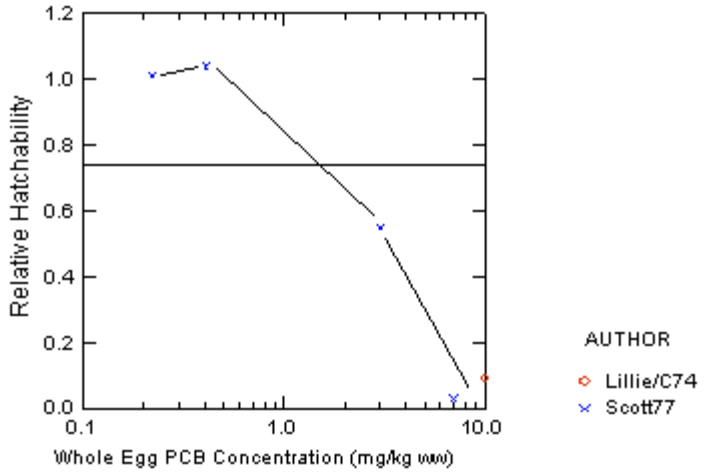


Figure 24. Hatchability, Aroclor 1254 Residues in Chicken Eggs

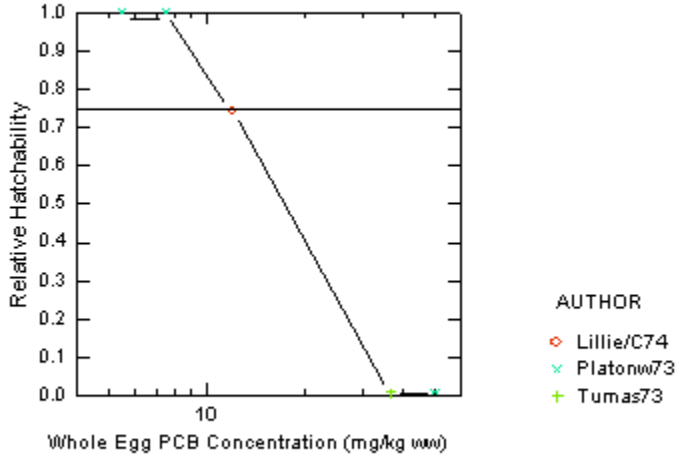


Figure 25. Chick Bodyweight, PCB Dose to Chicken Hens

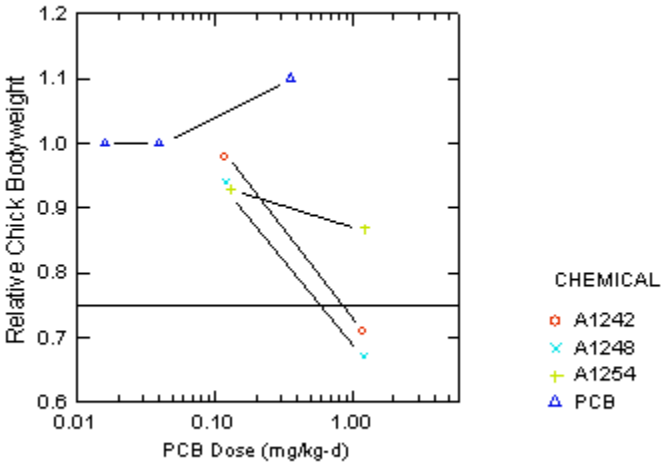


Figure 26. Chick Bodyweight, PCB Residues in Chicken Eggs

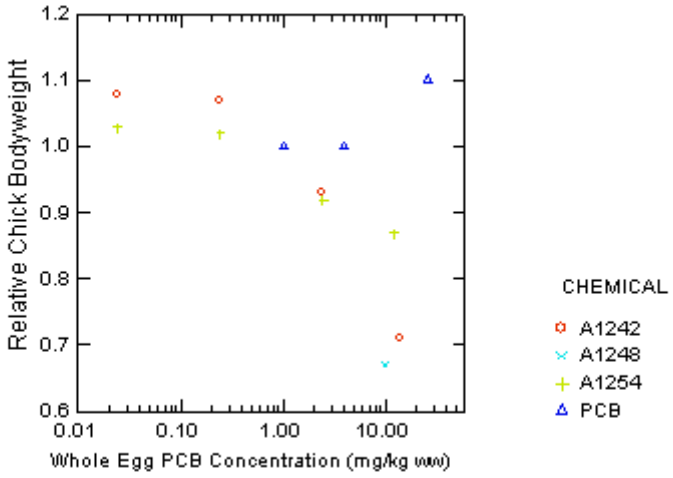


Figure 27. Chick Bodyweight, Aroclor 1242 Residues in Eggs

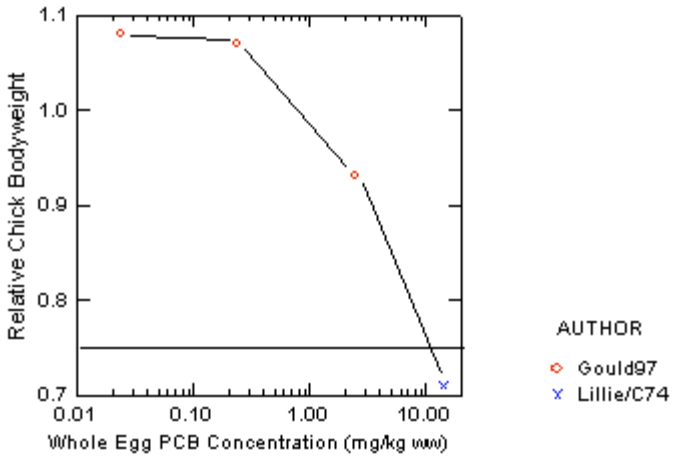


Figure 28. Chick Survival, PCB Dose to Chicken Hens

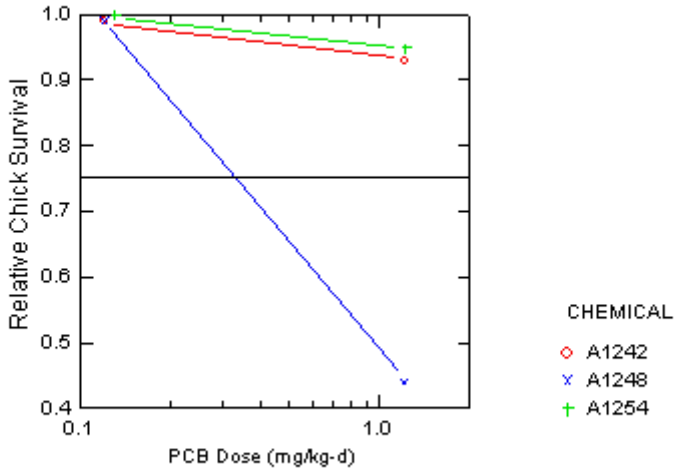


Figure 29. Egg Productivity, PCB Dose to Chicken Hens

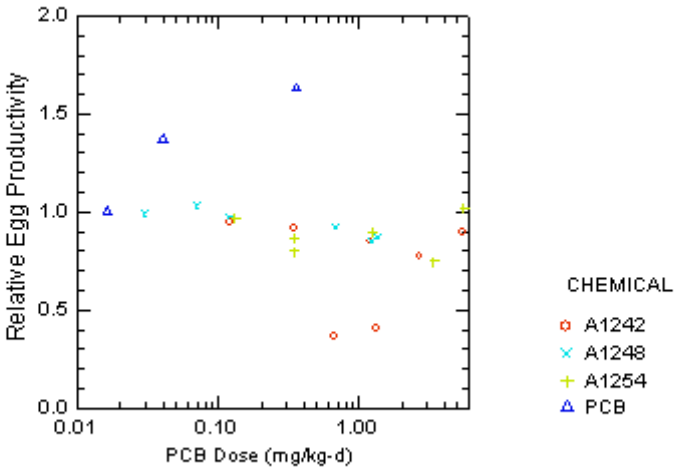


Figure 30. Egg Fertility, PCB Dose to Chicken Hens

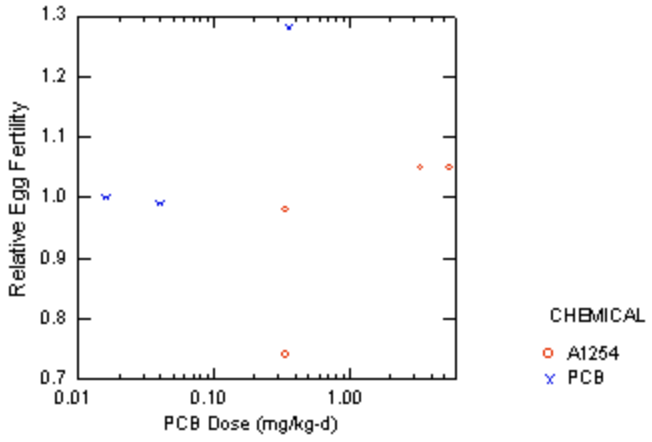


Figure 31. Chick Deformity, PCB Dose to Chicken Hens

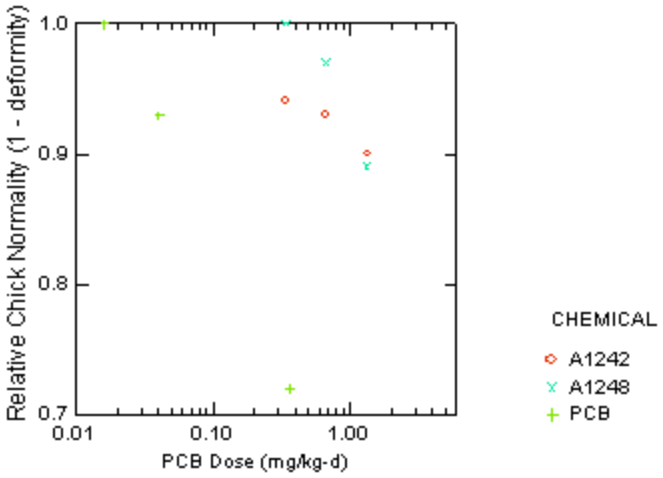


Figure 32. Chick Survival, PCB Residues in Chicken Eggs

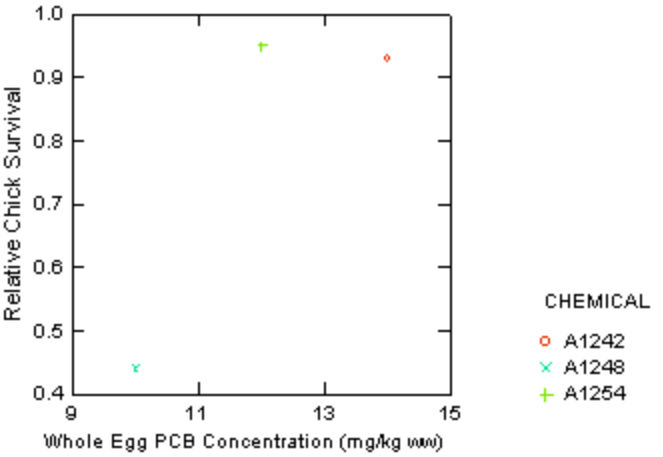


Table 2. Log-Linear Interpolation of PCB Toxicity Reference Values (TRV) for Mink

Chemical or Field study author	Response	Exposure Duration	Control RR	Treatment conc < TRV conc	Treatment conc < TRV RR	Treatment conc > TRV conc	Treatment conc > TRV RR	Target RR	P	TRV	Effect level	Study
			M_1	C_j	M_j	C_{j+1}	M_{j+1}					
Aroclor feeding studies												
A1242	live kit/ mated ♀	1 season	1	2	1.43	2.88	0.58	0.75		2.68	low effect	Aulerich77, Kakela02
			1	2	1.43	2.88	0.58	0.9		2.51	no effect	Aulerich77, Kakela02
A1254	live kit/ mated ♀	1 season	1	1	0.92	2	0.04	0.75		1.14	low effect	Wren87, Aulerich77
			1	1	0.92	2	0.04	0.9		1.02	no effect	Wren87, Aulerich77
A1254	kit bodywt	1 season	1	1	0.77	2	0.55	0.75		1.07	low effect	Wren87, Aulerich77
			1	0.02	1			0.9		>0.02	no effect	Wren87
A1254	kit survival	1 season	1	0.02	1	2	0	0.75		<1.00	low effect	Wren87, Aulerich77
			1	0.02	1			0.9		>0.02	no effect	Wren87
Comparison of 1 breeding season exposure vs 2 breeding seasons or generations continuous exposure												
A50	live kit/ mated ♀	1 season	1	2.31	0.92	12	0	0.75		3.13	low effect	Brunstm01, Kihistrm92
		1 season	1	2.31	0.92	12	0	0.9		2.39	no effect	Brunstm01, Kihistrm92
		2 season	1	0.77	1.27	2.31	0.2	0.75		1.31	low effect	Brunstm01
		2 season	1	0.77	1.27	2.31	0.2	0.9		1.13	no effect	Brunstm01
Ratio 2 season / 1 season			*0.47 no effect*									
Ratio 2 season / 1 season			*0.42 low effect*									
Restum	live kit/ mated ♀	1 season	1	1	0.91			0.75		>1.00	low effect	Restum98
		2 season	1	0.25	0.98	0.5	0.63	0.75		0.39	low effect	Restum98
		2 generation	1	0.25	0.84	0.5	0.23	0.75		0.28	low effect	Restum98
Ratio 2 season / 1 season			*<0.39 low effect*									
Ratio 2 generation / 1 season			*<0.28 low effect*									
Restum	kit bodywt	1 season	1	1	0.77			0.75		1.00	low effect	Restum98
		2 season	1	0.5	0.79	1	0.74	0.75		0.87	low effect	Restum98
		2 generation	1	0.25	0.87	0.5	0.69	0.75		0.40	low effect	Restum98
Ratio 2 season / 1 season			*0.87 low effect*									
Ratio 2 generation / 1 season			*0.40 low effect*									
Restum	kit survival	1 season	1	0.25	0.93	0.5	0.72	0.75		0.45	low effect	Restum98
		2 season	1	0.25	0.95	0.75	0.11	0.75		0.32	low effect	Restum98
		2 generation	1	0.25	0.8	0.5	0.18	0.75		0.26	low effect	Restum98
Ratio 2 season / 1 season			*0.72 low effect*									
Ratio 2 generation / 1 season			*0.58 low effect*									
Mean ratio 2 season or gen./ 1 season			*0.52 low effect*			(all studies)						

Notes for Table 2.

bodywt - bodyweight
conc - dietary concentration of PCBs (mg/kg wet weight (ww))
RR - relative response = treatment response / control response
Kit bodyweight is for birth to 1 week age.
TRV - toxicity reference value for dietary PCBs (mg/kg wet weight (ww))

$$\text{Log}_{10}\,\text{TRV} = \text{Log}_{10}\,C_j + (((M_1 * P) - M_j) * ((\text{Log}_{10}\,C_{j+1} - \text{Log}_{10}\,C_j) / (M_{j+1} - M_j)))$$

$$\text{TRV} = 10^{\,\text{Log10 TRV}}$$

Study - lead author, date; see notes for Table 4 for citations

A1254 live kit/mated 1 season M_j of 0.92 is the mean of 1.15 (Wren87) and 0.69 (Aulerich77) both at 1 mg/kg dietary concentration.
Restum kit survival 2 season M_j of 0.11 at C_j of 0.75 are the means of 0.05 and 0.16 (M_j) at 0.5 and 1.0 (C_j), respectively.

Table 3. Log-Linear Interpolation of PCB Toxicity Reference Values (TRV) for Chicken

Chemical	Response	Control	Treatment dose < TRV		Treatment dose > TRV		Target	TRV	Effect level	Study
		RR	dose	RR	dose	RR	RR			
		M_1	D_j	M_j	D_{j+1}	M_{j+1}	P			
Hen Dose (mg/kg$_{BW}$-d)										
A1242	hatchability	1	0.67	0.82	1.34	0.55	0.75	0.80	low effect	Britton73
A1242	hatchability	1	0.34	1.03	0.67	0.82	0.9	0.52	no effect	Britton73
A1242	hatchability	1	0.34	0.84	0.67	0.51	0.75	0.41	low effect	Lillie75
A1242	hatchability	1	0.12	0.98	0.34	0.84	0.9	0.13	no effect	Lillie/Cecil74
A1242	chick bw	1	0.12	0.98	1.21	0.71	0.75	0.86	low effect	Lillie/Cecil74
A1242	chick bw	1	0.12	0.98	1.21	0.71	0.9	0.24	no effect	Lillie/Cecil74
A1248	hatchability	1	0.34	0.96	0.67	0.55	0.75	0.48	low effect	Lillie75; Scott77
A1248	hatchability	1	0.34	0.96	0.67	0.55	0.9	0.38	no effect	Lillie75; Scott77
A1248	chick bw	1	0.12	0.94	1.21	0.67	0.75	0.61	low effect	Lillie/Cecil74
A1248	chick bw	1	0.12	0.94	1.21	0.67	0.9	0.17	no effect	Lillie/Cecil74
A1248	survival	1	0.12	0.99	1.21	0.44	0.75	0.33	low effect	Lillie/Cecil74
A1248	survival	1	0.12	0.99	1.21	0.44	0.9	0.18	no effect	Lillie/Cecil74
A1254	hatchability	1	0.34	1	1.22	0.74	0.75	1.16	low effect	Platonw73; Lillie/Cecil74
A1254	hatchability	1	0.34	1	1.22	0.74	0.9	0.56	no effect	Platonw73; Lillie/Cecil74
Egg Concentration (mg/kg, ww)			conc		conc					
		M_1	C_j	M_j	C_{j+1}	M_{j+1}	P	TRV	Effect level	Study
A1242	hatchability	1	1.35	0.82	2.26	0.55	0.75	1.54	low effect	Britton73
A1242	hatchability	1	0.62	1.03	1.35	0.82	0.9	1.00	no effect	Britton73
A1242	chick bw	1	2.44	0.93	14	0.71	0.75	10.19	low effect	Gould97; Lillie/Cecil74
A1242	chick bw	1	2.44	0.93	14	0.71	0.9	3.10	no effect	Gould97; Lillie/Cecil74
A1248	hatchability	1	0.41	1.04	3	0.55	0.75	1.33	low effect	Scott77
A1248	hatchability	1	0.41	1.04	3	0.55	0.9	0.72	no effect	Scott77
A1254	hatchability	1	7.5	1	12	0.74	0.75	11.79	low effect	Platonw73; Lillie/Cecil74
A1254	hatchability	1	7.5	1	12	0.74	0.9	8.99	no effect	Platonw73; Lillie/Cecil74

Notes for Table 3.

bw - bodyweight
conc - whole egg PCB concentration, mg/kg, ww
dose - bodyweight-normalized ingestion, mg PCB/kg$_{BW}$-d
RR - relative response = treatment response / control response
Study - lead author, date; see notes for Table 5 for citations
TRV - toxicity reference value for PCB dose (D) (mg/kg$_{BW}$-d) or whole egg concentration (C) (mg/kg wet weight (ww))

$$\text{Log}_{10}\,TRV = \text{Log}_{10}\,D_j + (((M_1 * P) - M_j) * ((\text{Log}_{10}\,D_{j+1} - \text{Log}_{10}\,D_j) / (M_{j+1} - M_j)))$$

$$\text{Log}_{10}\,TRV = \text{Log}_{10}\,C_j + (((M_1 * P) - M_j) * ((\text{Log}_{10}\,C_{j+1} - \text{Log}_{10}\,C_j) / (M_{j+1} - M_j)))$$

$$TRV = 10^{\,\text{Log10 TRV}}$$

Table 4. Mink PCB Toxicity Studies

Ref	Exposure				Relative Response Compared to Control					
	Chemical & Source	Exposure Duration	Dietary Conc	Tissue Conc	whelped ♀ / mated ♀	total kits / whelped ♀	live kits / whelped ♀	live kits / mated ♀	kit BW, time	kit survival, time
1	reported as A1254, from cow	5.2 month	0.64 mg/kg (control 0.3 mg/kg)	1.23 mg/kg liver (control 0.39 mg/kg); 0.97 mg/kg muscle (control 0.23 mg/kg)				0.17		0, 1 d
		3.4 month	3.6 mg/kg	11.99 mg/kg liver; 3.31 mg/kg muscle	0	0	0	0		
2	A1242 product	9.7 month	2 mg/kg (control NA)		1	1.37	1.43	1.43	0.94 birth	1.42 4 wk
	A1254 product	4.2 month	1 mg/kg (control NA)		0.8	0.90	0.86	0.69		
		9.7 month	2 mg/kg (control NA)		0.29	0.24	0.14	0.04	0.55 birth	0 4 wk
		4.2 month	5 mg/kg (control NA)		0.25	0.50	0.20	0.05		
3	NA (PCB type not identified)	2.2 month	3.3 mg/kg + 3.3 mg/kg DDT (control 0.05 mg/kg)	86 mg/kg fat (control 14 mg/kg)	0.79	0.57	0.20	0.17	0.72 birth	0.21 5 d

Ref	Exposure				Relative Response Compared to Control					
	Chemical & Source	Exposure Duration	Dietary Conc	Tissue Conc	whelped ♀ / mated ♀	total kits / whelped ♀	live kits / whelped ♀	live kits / mated ♀	kit BW, time	kit survival, time
			11 mg/kg	280 mg/kg fat	0	0	0	0		
4	A1242 product	8.1 month	5 mg/kg (control NA)		0	0	0	0		
			10 mg/kg		0	0	0	0		
5	reported as A1254, Green Bay alewife	7 month	0.21 mg/kg (control 0.09 mg/kg)	8.1 mg/kg adipose (control 2.9 mg/kg)	0.92	1.15	1.26	1.11	1.01 birth 1.02 4 wk	0.93 4 wk
	L Michigan Whitefish	7 month	0.48 mg/kg	13 mg/kg adipose	0.89	0.91	0.95	0.84	1.02 birth 0.88 4 wk	0.51 4 wk
	Saginaw Bay sucker	7 month	0.63 mg/kg	10 mg/kg adipose	1.00	0.80	0.67	0.66	1.05 birth 0.91 4 wk	0.73 4 wk
	L Erie perch	7 month	0.69 mg/kg	13 mg/kg adipose	0.91	0.93	0.88	0.79	0.98 birth 0.80 4 wk	0.65 4 wk
	Saginaw Bay carp	7 month	1.5 mg/kg	37 mg/kg adipose	0.30	0.56	0	0		
	Erie perch & Saginaw wht sucker	7 month	0.66 mg/kg (control 0.04 mg/kg)		0.58	0.37	0.19	0.11	0.86 birth	0 4 wk

Ref	Exposure				Relative Response Compared to Control					
	Chemical & Source	Exposure Duration	Dietary Conc	Tissue Conc	whelped ♀ / mated ♀	total kits / whelped ♀	live kits / whelped ♀	live kits / mated ♀	kit BW, time	kit survival, time
6	A1254 product	6.1 month	1 mg/kg (control 0.02 mg/kg)	2.8 mg/kg liver (control 0.09 mg/kg)	0.99	1.09	1.16	1.15	0.77 1 wk 0.75 3 wk, 0.71 5 wk	1.00 5 wk nearly all starvation (control 75 % trauma or infection, but no starvation)
7	Clophen A50	3 month	12 mg/kg	181 mg/kg fat 4.0 mg/kg muscle	0.11	0.12	0	0		
	A1254	3 month	10 mg/kg	74 mg/kg fat 1.3 mg/kg muscle	0.34	0.66	0	0		
8	PCB - sum of 1242, 1248, 1254, and 1260; TEQ - H4IIE bioassay; Saginaw carp	6 month	PCB 0.72 mg/kg (control 0.015 mg/kg); TEQ 19.4 pg/g (control 1 pg/g)	PCB 2.2 mg/kg liver (control 0.1 mg/kg) TEQ 495 pg/g (control <10 pg/g)	1.00	0.93	0.76	0.76	0.93 birth; 0.67 3 wk; 0.79 6 wk	0.33 6 wk
			PCB 1.53 mg/kg TEQ 40 pg/g	PCB 3.1 mg/kg liver TEQ 439 pg/g	1.00	1.02	0.96	0.96	0.82 birth; 0.67 3 wk 0.41 6 wk	0.13 6 wk

Ref	Exposure				Relative Response Compared to Control					
	Chemical & Source	Exposure Duration	Dietary Conc	Tissue Conc	whelped ♀ / mated ♀	total kits / whelped ♀	live kits / whelped ♀	live kits / mated ♀	kit BW, time	kit survival, time
			PCB 2.56 mg/kg TEQ 80.8 pg/g	PCB 6.3 mg/kg liver TEQ 656 pg/g	1.00	0.58	0.14	0.14	0.71 birth	0 3 wk
9	PCB - sum of 1242, 1248, 1254, and 1260; TEQ - H4IIE bioassay; Saginaw carp	6 month (P_1 1992)	PCB 0.25 mg/kg (control 0.02 mg/kg) TEQ 7.1 pg/g (control 1 pg/g)		1.36	1.16	1.19	1.66	0.93-0.94 birth 0.75-0.89 3 wk 0.75-0.85 6 wk	 1.06 3 wk 0.93 6 wk
			PCB 0.5 mg/kg TEQ 13.6 pg/g		1.35	1.02	0.91	1.25	0.84-0.87 birth 0.67-0.75 3 wk 0.65-0.68 6 wk	 0.81 3 wk 0.72 6 wk
			PCB 1.0 mg/kg TEQ 26.4 pg/g		1.16	1.02	0.77	0.91	0.75-0.79 birth 0.51-0.59 3 wk 0.35-0.49 6 wk	 0.32 3 wk 0.32 6 wk
		16 month (P_1 1993)	PCB 0.25 mg/kg TEQ 7.1 pg/g	PCB 0.98 mg/kg liver (control 0.07 mg/kg)	1.02	0.95	0.96	0.98	0.88-1.09 birth 0.87-0.91 3 wk 0.92 6 wk	 0.99 3 wk 0.95 6 wk

Ref	Exposure				Relative Response Compared to Control					
	Chemical & Source	Exposure Duration	Dietary Conc	Tissue Conc	whelped ♀ / mated ♀	total kits / whelped ♀	live kits / whelped ♀	live kits / mated ♀	kit BW, time	kit survival, time
			PCB 0.5 mg/kg TEQ 13.6 pg/g	PCB 0.89 mg/kg liver	0.78	0.92	0.80	0.63	0.77-0.81 birth 0.65-0.67 3 wk 0.93 6wk	 0.62 3 wk 0.05 6 wk
			PCB 1.0 mg/kg TEQ 26.4 pg/g	PCB 1.57 mg/kg liver	0.66	0.63	0.59	0.40	0.73-0.74 birth 0.50-0.59 3 wk 0.60-0.66 6 wk	 0.15 3 wk 0.16 6 wk
		12 month F_1 of 6-month exposed parents (F_1-1 1993)	PCB 0.25 mg/kg TEQ 7.1 pg/g	PCB 0.63 mg/kg liver (control 0.02 mg/kg)	0.85	1.05	0.96	0.84	0.87 birth 1.03-1.10 3 wk 0.89-0.95 6 wk	 0.76 3 wk 0.80 6 wk
			PCB 0.5 mg/kg TEQ 13.6 pg/g	PCB 0.96 mg/kg liver	0.76	0.88	0.31	0.23	0.64-0.73 birth 0.42 3 wk 0.54 6 wk	 0.16 3 wk 0.18 6 wk
			PCB 1.0 mg/kg TEQ 26.4 pg/g	1.47	0.63	0.53	0.09	0.07	0.51-0.60 birth	0 3 wk

Ref	Exposure				Relative Response Compared to Control					
	Chemical & Source	Exposure Duration	Dietary Conc	Tissue Conc	whelped ♀ / mated ♀	total kits / whelped ♀	live kits / whelped ♀	live kits / mated ♀	kit BW, time	kit survival, time
10	reported as A1260 Poplar Creek & Clinch River fish	7 month	0.52 mg/kg (control <0.005 mg/kg)	<0.005 mg/kg liver (control <0.005); NA fat (control 3.2 mg/kg fat)	0.58	1.20	1.15	0.67	1.02 6 wk	0.79 6 wk
			1.01 mg/kg	<0.005 mg/kg liver; 105.86 mg/kg fat	0.87	0.92	1.10	0.96	0.94 6 wk	1.24
			1.36 mg/kg	7.25 mg/kg liver; 128.63 mg/kg fat	1.16	0.66	0.75	0.87	0.90 6 wk	1.57
11	Clophen A50 product; TEQ calculated by WHO TEFs	6 month	PCB 0.77 mg/kg (control 0.01 mg/kg) TEQ 22 pg/g		0.96	1.20	1.30	1.24	0.99 birth	
			PCB 2.31 mg/kg TEQ 65 pg/g		0.97	1.04	0.95	0.92	0.82 birth	
		18 month	PCB 0.77 mg/kg TEQ 22 pg/g (NOAEC TEQ 3 pg/g)	11 mg/kg lipid muscle (control <1 mg/kg)	0.95	1.22	1.34	1.27	0.90 birth 0.69 2 wk 0.67 5 wk	0.49 2 wk

Ref	Exposure				Relative Response Compared to Control					
	Chemical & Source	Exposure Duration	Dietary Conc	Tissue Conc	whelped ♀ / mated ♀	total kits / whelped ♀	live kits / whelped ♀	live kits / mated ♀	kit BW, time	kit survival, time
			PCB 2.31 mg/kg TEQ 65 pg/g	54 mg/kg	0.42	0.80	0.45	0.20	0.75 birth	0 2 wk
12	reported as PCB (Aroclor not specified); Baltic herring	5.3 month before mating + exposure during mating; TEQ not specified ("internat-ional" TEFs)	PCB 0.36 mg/kg (control 0.024 mg/kg) TEQ 26 pg/g (control 2 pg/g)		1.00	0.92	0.92	0.92	0.87–0.90 10 d 0.87–0.89 50 d	
	A1242 product added to freshwater smelt	5.3 month before mating, control exposure during mating	PCB 2.88 mg/kg TEQ 157 pg/g		0.80	0.76	0.73	0.58	0.78-0.81 10 d 0.95–1.01 50 d	

Notes for Table 4.

Ref - references [abbreviated reference used in the figures and Table 2 in brackets]:

1) Platonow and Karstad. 1973. [Platonow73]
2) Aulerich and Ringer. 1977. [Aulerich77]
3) Jensen 1977. [Jensen77]
4) Bleavins, et al. 1980 [Bleavins80]

5) Hornshaw, et al. 1983. [Hornshw83]
6) Wren, et al. 1987 [Wren87]
7) Kihiström, et al. 1992. [Kihistrm92]
8) Heaton, et al. 1995a, 1995b, and Tillitt, et al. 1996. [Heaton95]
9) Restum, et al. 1998, Shipp, et al. 1998, and Tillitt, et al. 1996. [Restum98]
10) Halbrook, et al. 1999. [Halbrok99]
11) Brunström, et al. 2001. [Brunstm01]
12) Käkelä, et al. 2002. [Kakela02]

Relative Response Compared to Control = treatment response / control response

Source: product is commercial product mixed with food; field is field-contaminated biota prepared as food

TEQ for Restum, et al. (1998) is based on the following regression of total PCB (mg/kg) and H4IIE-bioassay TEQ (pg/g) (data from Tillitt, et al. 1996):

TEQ = (25.735 * PCB) + 0.703 $r^2 = 1.0, p = 0.005$, for PCB range 0.015–1.53 mg/kg

Table 5. Chicken PCB Toxicity Studies

Ref	Exposure					Relative Response Compared to Control					
	Chemical, Source	Species	Exposure Duration	Dose to Hen (mg/kg-d)	Egg Conc (whole ww)	Egg Productivity	Egg Fertility	Hatchability	Chick BW	Chick Survival	Chick Normality
1	A1242 product	chicken (white leghorn)	6 wk	1.34				0.10, 6 wk			
				3.35				0, 6 wk			
		chicken (broiler)		1.34				0.09, 6 wk			
				3.35				0.07, 6 wk			
2	A1242 product	chicken (white leghorn)	6 wk	0.34 (control NA)	0.62 mg/kg 6 wk	0.92, 6 wk		1.03, 6 wk			
				0.67	1.35 mg/kg 6 wk	0.36 6 wk		0.82 6 wk			
				1.34	2.26 mg/kg 6 wk	0.41 6 wk		0.55 6 wk			
				2.68	2.8 mg/kg 6 wk	0.77 6 wk		0 6 wk			
				5.36	10.01 mg/kg 6 wk	0.90 6 wk		0 6 wk			
3	A1254 product	chicken (white leghorn)	14 wk	0.34 (control NA)	5.5 mg/kg (max.) 2-14 wk	0.87 1-14 wk	0.98 1-14 wk	1 1-14 wk			
			39 wk	0.34	7.5 mg/kg (max.) 26-35 wk	0.80 26-39 wk	0.74 34-39 wk	1 1-39 wk			

Ref	Exposure					Relative Response Compared to Control					
	Chemical, Source	Species	Exposure Duration	Dose to Hen (mg/kg-d)	Egg Conc (whole ww)	Egg Productivity	Egg Fertility	Hatchability	Chick BW	Chick Survival	Chick Normality
			14 wk	3.35	50 mg/kg (max.) 2-14 wk	0.75 1-14 wk	1.05 1-14 wk	0 3-6 wk			
4	A1254 product	chicken (white leghorn)	6 wk	5.5 (control NA)	10 mg/kg 1 wk; 24 mg/kg 2 wk; 36.4 mg/kg 3 wk; (control NA)	1.02 1-6 wk	1.05 1-6 wk	0.41 2 wk; 0 3-6 wk			
5	A1221 product	chicken (white leghorn)	9 wk	1.30 (control NA)	<1 mg/kg 9 wk	1 0-9 wk		0.99 0-9 wk	0.98 6-9 wk	1	
	A1232 product			1.34	2.5 mg/kg 9 wk	0.91 0-9 wk		0.60 0-9 wk 0.43 8 wk	0.85 6-9 wk	0.93	
	A1242 product			0.12		0.95 0-9 wk		0.98 0-9 wk	0.98 6-9 wk	0.99	
				1.21	14 mg/kg 9 wk	0.85 0-9 wk		0.20 0-9 wk 0.10 8 wk	0.71 6-9 wk	0.93	
	A1248 product			0.12		0.97 0-9 wk		0.99 0-9 wk	0.94 6-9 wk	0.99	

Ref	Exposure					Relative Response Compared to Control					
	Chemical, Source	Species	Exposure Duration	Dose to Hen (mg/kg-d)	Egg Conc (whole ww)	Egg Productivity	Egg Fertility	Hatchability	Chick BW	Chick Survival	Chick Normality
				1.21	10 mg/kg 9 wk	0.85 0-9 wk		0.13 0-9 wk 0.09 8 wk	0.67 6-9 wk	0.44	
	A1254 product			0.13		0.97 0-9 wk		0.96 0-9 wk	0.93 6-9 wk	1	
				1.22	12 mg/kg	0.90 0-9 wk		0.86 0-9 wk 0.74 8 wk	0.87 6-9 wk	0.95	
	A1268 product			1.28	23 mg/kg	0.94 0-9 wk		0.98 0-9 wk	0.96 6-9 wk	1	
6	A1232 product	chicken (white leghom)	8 wk	0.67 (control NA)				0.86 8 wk			
				1.34				0.57, 8 wk			
	A1242 product			0.34				0.84, 0-8 wk			0.94
				0.67				0.74, 0-8 wk 0.51, 8 wk			0.93
				1.34				0.31, 0-8 wk 0.06, 8 wk			0.90
	A1248 product			0.34				0.96, 0-8 wk			1
				0.67				0.75, 0-8 wk 0.42, 8 wk			0.97

Ref	Exposure					Relative Response Compared to Control					
	Chemical, Source	Species	Exposure Duration	Dose to Hen (mg/kg-d)	Egg Conc (whole ww)	Egg Productivity	Egg Fertility	Hatchability	Chick BW	Chick Survival	Chick Normality
				1.34				0.24, 0-8 wk 0.06, 8 wk			0.89
7	A1248 product	chicken (white leghorn)	8 wk	0.03 (control NA)	0.16 mg/kg 4 wk; 0.22 mg/kg 8 wk	0.99 8 wk		1.01 4 wk 1.01 8 wk			
				0.07	0.33 mg/kg 4 wk; 0.41 mg/kg 8 wk	1.03 8 wk		0.98 4 wk 1.04 8 wk			
				0.67	2.2 mg/kg 4 wk; 3 mg/kg 8 wk	0.92 8 wk		0.73 4 wk 0.55 8 wk			
				1.34	4.5 mg/kg 4 wk; 7 mg/kg 8 wk	0.87 8 wk		0.03 4 wk 0.03 8 wk			
8	reported as A1242, 1248, 1254 and 1260; H4IIE bioassay TEQ; Saginaw Bay carp	chicken (white leghorn)	8 wk	PCB 0.04 (control 0.016); TEQ 1.4 ng/kg-d (control 0.2)	4 mg/kg 4-8 wk (control 1 mg/kg)	1.37 4-8 wk	0.99 4-8 wk	1.05 4-8 wk	1.0 hatch		0.93 -1 to 8 wk

Ref	Exposure					Relative Response Compared to Control					
	Chemical, Source	Species	Exposure Duration	Dose to Hen (mg/kg-d)	Egg Conc (whole ww)	Egg Productivity	Egg Fertility	Hatchability	Chick BW	Chick Survival	Chick Normality
				PCB 0.36; TEQ 3.2	26 mg/kg 4-8 wk	1.63 4-8 wk	1.28 4-8 wk	0.82 4-8 wk	1.1 hatch		0.72 -1 to 8 wk
9	A1242 product	chicken eggs (white leghom)	injected in yolk		0.02 mg/kg (control NA)				1.08 embryo		
					0.24 mg/kg				1.07 embryo		
					2.44 mg/kg				0.93 embryo		
	A1254 product				0.02 mg/kg				1.03 embryo		
					0.24 mg/kg				1.02 embryo		
					2.44 mg/kg				0.92 embryo		

Notes for Table 5.

Ref - references [abbreviated reference used in the figures and Table 2 in brackets]:

1) Briggs and Harris. 1972. [Briggs72]
2) Britton and Huston. 1973. [Britton73]
3) Platonow and Reinhart. 1973. [Platonw73]
4) Tumasonis, et al. 1973. [Tumas73]
5) Lillie, et al. 1974 and Cecil, et al. 1974. [Lillie/Cecil74 or Lillie/C74]
6) Lillie, et al. 1975. [Lillie75]

7) Scott 1977. [Scott77]
8) Summer, et al. 1996a., 1996b. [Summer96]
9) Gould, et al. 1997. [Gould97]

Exposures occur through contaminated feed except for Tumasonis, et al. (1973) through contaminated water, and Gould, et al. (1997) through yolk injection.

Relative Response Compared to Control = treatment response / control response

Source: product is commercial product mixed with feed or in water; field is field-contaminated biota prepared as feed

Dose: Calculated from experimental data when available. Generic calculation based on a white leghorn hen food ingestion rate of 0.067 kg feed/kg_{BW}-d (Medway and Kare 1959 cited in USEPA 1995a).

Egg Concentration: Yolk concentration is converted to whole-egg concentration by multiplying by 0.364 (Southerland and Rahn 1987 as cited in Hoffman, et al. 1996).

Chick normality is the proportion of chicks without deformities (= 1 - deformity rate)

Table 6. Summary of Mink PCB Studies and Relative Responses

Lead author Date	Chemical	Dietary PCB conc. mg/kg ww	Treatment name	Chemical source	Dietary TEQ conc. pg/g ww	TEQ source	Exposure duration month	Breeding seasons exposed	Generations exposed	Tissue	Tissue residue PCB conc. mg/kg ww	Lipid cont. % ww	PCB conc. mg/kg lw	TEQ conc. ww	Whelp frequency Control %	Treatment %	RR ratio	Whelp freq. source
Platonow73	A1254	0.64		field			5.2	1	1	liver, muscle	1.23, 0.97							
Platonow73	A1254	3.57		field			3.4	1	1	liver, muscle	11.99, 3.31				NA	0	0.00	text p 393
Aulerich77	A1242	2		product			9.7	1	1						100	100	1.00	table 10
Aulerich77	A1254	1		product			4.2	1	1						100	80	0.80	table 9
Aulerich77	A1254	2		product			9.7	1	1						100	29	0.29	table 10
Aulerich77	A1254	5		product			4.2	1	1						100	25	0.25	table 9
Jensen77	NA	3.3	Group B	NA			2.2	1	1	adipose			86		92	73	0.79	table 1
Jensen77	NA	11	Goup C	NA			2.2	1	1	adipose			280		92	0	0.00	table 1
Bleavins80	A1242	5		product			8.1	1	1						76.2	0	0.00	table 2
Bleavins80	A1242	10		product			8.1	1	1						76.2	0	0.00	table 2
Hornshw83	A1254	0.21	alewife	field			7	1	1	adipose			8.1		90	83	0.92	table 3
Hornshw83	A1254	0.48	whitefish	field			7	1	1	adipose			13		90	80	0.89	table 3
Hornshw83	A1254	0.63	sucker	field			7	1	1	adipose			10		90	90	1.00	table 3
Hornshw83	A1254	0.69	perch	field			7	1	1	adipose			13		90	82	0.91	table 3
Hornshw83	A1254	1.5	carp	field			7	1	1	adipose			37		90	27	0.30	table 3
Hornshw83	A1254	0.66	perch/sucker	field			7	1	1						86	50	0.58	table 3
Wren87	A1254	1	PCB	product			6.1	1	1	liver	2.8				93	92	0.99	87b table 2
Kihistrm92	A50	12	Group 2	product			3	1	1	muscle	3.98	2.2	181.00		90	10	0.11	table 2
Kihistrm92	A1254	10	Group 9	product			3	1	1	muscle	1.33	1.8	74.00		89	30	0.34	table 2
Heaton95	PCB	0.72	10 % carp	field	19.4	H4IIE	6	1	1	liver	2.2			495	50	50	1.00	p 335, table 2
Heaton95	PCB	1.53	20 % carp	field	40	H4IIE	6	1	1	liver	3.1			439	50	50	1.00	p 335, table 2
Heaton95	PCB	2.56	30 % carp	field	80.8	H4IIE	6	1	1	liver	6.3			656	50	50	1.00	p 335, table 2
Restum98	PCB	0.25	P1 0.25 to F1-1	field	7.1	H4IIE	6	1	1						69	94	1.36	table 6
Restum98	PCB	0.5	P1 0.5 to F1-1	field	13.6	H4IIE	6	1	1						69	93	1.35	table 6
Restum98	PCB	1	P1 1.0 to F1-1	field	26.4	H4IIE	6	1	1						69	80	1.16	table 6
Restum98	PCB	0.25	P1 0.25-0.25 to F1-2	field	7.1	H4IIE	16	2	1	liver	0.98				86	88	1.02	table 6
Restum98	PCB	0.5	P1 0.5-0.5 to F1-2	field	13.6	H4IIE	16	2	1	liver	0.89				86	67	0.78	table 6
Restum98	PCB	1	P1 1.0-1.0 to F1-2	field	26.4	H4IIE	16	2	1	liver	1.57				86	57	0.66	table 6
Restum98	PCB	0.25	F1-1 0.25-0.25 to F2	field	7.1	H4IIE	12	2	2	liver	0.63				79	67	0.85	table 6
Restum98	PCB	0.5	F1-1 0.5-0.5 to F2	field	13.6	H4IIE	12	2	2	liver	0.96				79	60	0.76	table 6
Restum98	PCB	1	F1-1 1.0-1.0 to F2	field	26.4	H4IIE	12	2	2	liver	1.47				79	50	0.63	table 6
Halbrok99	A1260	0.52	Diet C	field			7	1	1	liver	<0.005				86	50	0.58	text p 652, table 2
Halbrok99	A1260	1.01	Diet D	field			7	1	1	liver, fat	<0.005		105.86		86	75	0.87	text p 652, table 2
Halbrok99	A1260	1.36	Diet E	field			7	1	1	liver, fat	7.25		128.63		86	100	1.16	text p 652, table 2
Brunstm01	A50	0.77	A50 low	product	22	WHO	6	1	1						93	89	0.96	table 3
Brunstm01	A50	2.31	A50 high	product	65	WHO	6	1	1						93	90	0.97	table 3
Brunstm01	A50	0.77	A50 low	product	22	WHO	18	2	1	muscle	0.26	2.4	11		93	88	0.95	table 5
Brunstm01	A50	2.31	A50 high	product	65	WHO	18	2	1	muscle	1.30	2.4	54		93	39	0.42	table 5
Kakela02	PCB	0.36	Baltic herring	field	26	NA	5.3	1	1						100	100	1.00	table 3
Kakela02	A1242	2.88	Smelt PCB	product	157	NA	5.3	1	1						100	80	0.80	table 3

Notes:
Treatment data only, control data excluded (control RR = 1.0 by definition)
TEQ source - H4IIE - rat hepatoma cell bioassay; WHO - Van den Berg, et al. (1998)
Exposure duration - month = days / 30.5 or weeks / 4; PCB - sum of multiple Aroclors; NA - not available
RR - relative response = treatment response / control response
Default Live kits/mated female = Live kits/whelped female * fraction of females whelped
Plantonow73 - Treatment 0.64 Live kits/mated female = 3 kits / 10 females surviving (2 deaths out of 12 during breeding)
Jensen77 - PCB type or source not identified; Live kits/whelped female = No. of whelps born/pregnant female - number of stillbirths/bitch
Hornshaw83 - Tissue residue for February 1980, mean values
Kihistrm92 - Dietary PCB conc. = 2 mg A50/d or 1.64 mg A1254/d / 0.17 kg food/d (p. 564); Table 2 Stillborn should be 1 (not 100) for Group 2 (fig 4)
Heaton95 - Liver conc. from Tillitt, et al. 96 (Table 4)
Restum98 - Treatment name is parental designation to offspring designation; TEQ interpolated from Tillitt, et al. 96 (Tables 1 and 2)
Restum98 - Live kits/whelped female = Survivability at birth * Litter size
Restum98 - Kit bodyweight in order of male, female kit; -- no survivors; RR is the unweighted mean of male and female RRs, or single sex RR if only one sex survived
Halbrook99 - Diet A is used for control; Kit survival = (Alive at 6 weeks / Born alive) * 100
Brunstm01 - Dietary PCB conc. = 0.1 or 0.3 mg A50/d / 0.13 kg/d food ration (p. 2319)
Kakela02 - Smelt PCB treatment was exposed for 21 wk before breeding, then switched to control diet during breeding
Kakela02 - Dietary PCB conc. = Sum PCB per day / Average food consumption; Kit bodyweight in order of male kit, female kit; RR is unweighted mean
Kakela02 - Live kits/whelped female = ((Kits/mother * surviving females) - Dead kits) / surviving females; TEQ - "international" TEFs but no date is given

Table 6. Summary of Mink PCB Studies and Relative Responses

Lead author Date	Chemical	Dietary PCB conc. mg/kg ww	Treatment name	Total kits / whelped female Control number	Treatment number	RR ratio	Total kits / whelped source	Live kits / whelped female Control number	Treatment number	RR ratio	Live kits / whelped source	Live kits / mated female Control number	Treatment number	RR ratio	Live kits / mated source	Kit bodyweight 0-1 wk Control g	Treatment g	RR ratio
Platonow73	A1254	0.64										1.8	0.3	0.17	text p 393, 398			
Platonow73	A1254	3.57		NA	0	0.00	text p 393	NA	0	0.00	text p 393	1.8	0	0.00	text p 393, 398			
Aulerich77	A1242	2		4.1	5.6	1.37	table 10	3.5	5	1.43	table 10	3.5	5	1.43	table 10	9.9	9.3	0.94
Aulerich77	A1254	1		6	5.4	0.90	table 9	5.1	4.4	0.86	table 9	5.1	3.5	0.69	table 9			
Aulerich77	A1254	2		4.1	1	0.24	table 10	3.5	0.5	0.14	table 10	3.5	0.14	0.04	table 10	9.9	5.4	0.55
Aulerich77	A1254	5		6	3	0.50	table 9	5.1	1	0.20	table 9	5.1	0.25	0.05	table 9			
Jensen77	NA	3.3	Group B	5.1	2.9	0.57	table 1	4.6	0.9	0.20	text, table 1	4.2	0.7	0.17	text, table 1	9.4	6.8	0.72
Jensen77	NA	11	Goup C	5.1	0	0.00	table 1	4.6	0	0.00	text, table 1	4.2	0	0.00	text, table 1			
Bleavins80	A1242	5		5.8	0	0.00	table 2	4.9	0	0.00	table 2	3.8	0	0.00	table 2			
Bleavins80	A1242	10		5.8	0	0.00	table 2	4.9	0	0.00	table 2	3.8	0	0.00	table 2			
Hornshw83	A1254	0.21	alewife	5.4	6.2	1.15	table 3	4.2	5.3	1.26	table 3	3.8	4.2	1.11	table 3	8.3	8.4	1.01
Hornshw83	A1254	0.48	whitefish	5.4	4.9	0.91	table 3	4.2	4	0.95	table 3	3.8	3.2	0.84	table 3	8.3	8.5	1.02
Hornshw83	A1254	0.63	sucker	5.4	4.3	0.80	table 3	4.2	2.8	0.67	table 3	3.8	2.5	0.66	table 3	8.3	8.7	1.05
Hornshw83	A1254	0.69	perch	5.4	5	0.93	table 3	4.2	3.7	0.88	table 3	3.8	3	0.79	table 3	8.3	8.1	0.98
Hornshw83	A1254	1.5	carp	5.4	3	0.56	table 3	4.2	0	0.00	table 3	3.8	0	0.00	table 3			
Hornshw83	A1254	0.66	perch/sucker	5.4	2	0.37	table 3	5.2	1	0.19	table 3	4.4	0.5	0.11	table 3	9	7.7	0.86
Wren87	A1254	1	PCB	6.9	7.5	1.09	87b table 2	5.8	6.7	1.16	87b table 2	5.4	6.2	1.15	87b table 2	28.1	21.6	0.77
Kihistrm92	A50	12	Group 2	8.1	1	0.12	table 2	5.3	0	0.00	table 2	4.8	0	0.00	table 2			
Kihistrm92	A1254	10	Group 9	5	3.3	0.66	table 2	4.3	0	0.00	table 2	3.7	0	0.00	table 2			
Heaton95	PCB	0.72	10 % carp	5.7	5.3	0.93	table 2	5	3.8	0.76	table 2	2.5	1.9	0.76	p 335, table 2	10.5	9.76	0.93
Heaton95	PCB	1.53	20 % carp	5.7	5.8	1.02	table 2	5	4.8	0.96	table 2	2.5	2.4	0.96	p 335, table 2	10.5	8.66	0.82
Heaton95	PCB	2.56	30 % carp	5.7	3.3	0.58	table 2	5	0.7	0.14	table 2	2.5	0.35	0.14	p 335, table 2	10.5	7.49	0.71
Restum98	PCB	0.25	P1 0.25 to F1-1	5	5.8	1.16	table 6	4.7	5.6	1.19	tables 6, 7	3.2	5.3	1.66	table 6	10, 9.2	9.3, 8.7	0.94
Restum98	PCB	0.5	P1 0.5 to F1-1	5	5.1	1.02	table 6	4.7	4.3	0.91	tables 6, 7	3.2	4	1.25	table 6	10, 9.2	8.7, 7.7	0.86
Restum98	PCB	1	P1 1.0 to F1-1	5	5.1	1.02	table 6	4.7	3.6	0.77	tables 6, 7	3.2	2.9	0.91	table 6	10, 9.2	7.5, 7.3	0.77
Restum98	PCB	0.25	P1 0.25-0.25 to F1-2	6.3	6	0.95	table 6	5.6	5.4	0.96	tables 6, 7	4.8	4.7	0.98	table 6	11.1, 9.9	9.8, 10.8	0.99
Restum98	PCB	0.5	P1 0.5-0.5 to F1-2	6.3	5.8	0.92	table 6	5.6	4.5	0.80	tables 6, 7	4.8	3	0.63	table 6	11.1, 9.9	8.6, 8.0	0.79
Restum98	PCB	1	P1 1.0-1.0 to F1-2	6.3	4	0.63	table 6	5.6	3.3	0.59	tables 6, 7	4.8	1.9	0.40	table 6	11.1, 9.9	8.1, 7.3	0.74
Restum98	PCB	0.25	F1-1 0.25-0.25 to F2	5.7	6	1.05	table 6	5.5	5.3	0.96	tables 6, 7	4.3	3.6	0.84	table 6	9.8, 9.2	8.5, 8.0	0.87
Restum98	PCB	0.5	F1-1 0.5-0.5 to F2	5.7	5	0.88	table 6	5.5	1.7	0.31	tables 6, 7	4.3	1	0.23	table 6	9.8, 9.2	7.2, 5.9	0.69
Restum98	PCB	1	F1-1 1.0-1.0 to F2	5.7	3	0.53	table 6	5.5	0.5	0.09	tables 6, 7	4.3	0.3	0.07	table 6	9.8, 9.2	5.0, 5.5	0.56
Halbrok99	A1260	0.52	Diet C	6.5	7.8	1.20	table 2	5.2	6	1.15	table 2	4.5	3	0.67	text p 652, table 2			
Halbrok99	A1260	1.01	Diet D	6.5	6	0.92	table 2	5.2	5.7	1.10	table 2	4.5	4.3	0.96	text p 652, table 2			
Halbrok99	A1260	1.36	Diet E	6.5	4.3	0.66	table 2	5.2	3.9	0.75	table 2	4.5	3.9	0.87	text p 652, table 2			
Brunstm01	A50	0.77	A50 low	4.9	5.9	1.20	table 3	4	5.2	1.30	table 3	3.7	4.6	1.24	table 3	9.6	9.5	0.99
Brunstm01	A50	2.31	A50 high	4.9	5.1	1.04	table 3	4	3.8	0.95	table 3	3.7	3.4	0.92	table 3	9.6	7.9	0.82
Brunstm01	A50	0.77	A50 low	5.1	6.2	1.22	table 5	4.4	5.9	1.34	table 5	4.1	5.2	1.27	table 5	8.9	8	0.90
Brunstm01	A50	2.31	A50 high	5.1	4.1	0.80	table 5	4.4	2	0.45	table 5	4.1	0.8	0.20	table 5	8.9	6.7	0.75
Kakela02	PCB	0.36	Baltic herring	6.6	6.1	0.92	table 3	6.6	6.1	0.92	table 3	6.6	6.1	0.92	table 3			
Kakela02	A1242	2.88	Smelt PCB	6.6	5	0.76	table 3	6.6	4.8	0.73	table 3	6.6	3.8	0.58	table 3			

Table 6. Summary of Mink PCB Studies and Relative Responses

Lead author Date	Chemical	Dietary PCB conc. mg/kg ww	Treatment name	Kit bodyweight 2-3 wk Control g	Kit bodyweight 2-3 wk Treatment g	Kit bodyweight 2-3 wk RR ratio	Kit bodyweight 4-6 wk Control g	Kit bodyweight 4-6 wk Treatment g	Kit bodyweight 4-6 wk RR ratio	Kit bodyweight source	Kit survival Control %	Kit survival Treatment %	Kit survival RR ratio	Kit survival source
Platonow73	A1254	0.64									NA	0	0.00	text p 393
Platonow73	A1254	3.57												
Aulerich77	A1242	2								table 10	64	91	1.42	table 10
Aulerich77	A1254	1												
Aulerich77	A1254	2								table 10	64	0	0.00	table 10
Aulerich77	A1254	5												
Jensen77	NA	3.3	Group B							text	82	17	0.21	text
Jensen77	NA	11	Goup C											
Bleavins80	A1242	5												
Bleavins80	A1242	10												
Hornshw83	A1254	0.21	alewife				122	124	1.02	table 4	55	51	0.93	table 3
Hornshw83	A1254	0.48	whitefish				122	107	0.88	table 4	55	28	0.51	table 3
Hornshw83	A1254	0.63	sucker				122	111	0.91	table 4	55	40	0.73	table 3
Hornshw83	A1254	0.69	perch				122	98	0.80	table 4	55	36	0.65	table 3
Hornshw83	A1254	1.5	carp											
Hornshw83	A1254	0.66	perch/sucker							table 4	65	0	0.00	table 3
Wren87	A1254	1	PCB	107.3	80.2	0.75	227.8	161.2	0.71	87b table 4	72	72.2	1.00	87b table 2
Kihistrm92	A50	12	Group 2											
Kihistrm92	A1254	10	Group 9											
Heaton95	PCB	0.72	10 % carp	98.7	66.1	0.67	248	197	0.79	table 3	85	28	0.33	table3
Heaton95	PCB	1.53	20 % carp	98.7	65.8	0.67	248	101	0.41	table 3	85	11	0.13	table3
Heaton95	PCB	2.56	30 % carp							table 3	85	0	0.00	table3
Restum98	PCB	0.25	P1 0.25 to F1-1	113, 99	89, 88	0.84	293, 253	220, 214	0.80	table 8	72.7	67.8	0.93	table 7 wk 6
Restum98	PCB	0.5	P1 0.5 to F1-1	113, 99	76, 74	0.71	293, 253	200, 165	0.67	table 8	72.7	52.5	0.72	table 7 wk 6
Restum98	PCB	1	P1 1.0 to F1-1	113, 99	58, 58	0.55	293, 253	102, 125	0.42	table 8	72.7	23	0.32	table 7 wk 6
Restum98	PCB	0.25	P1 0.25-0.25 to F1-2	116, 110	106, 96	0.89	340, 304	312, 280	0.92	table 9	80.3	76.2	0.95	table 7 wk 6
Restum98	PCB	0.5	P1 0.5-0.5 to F1-2	116, 110	78, 72	0.66	340, 304	317, --	0.93	table 9	80.3	4.4	0.05	table 7 wk 6
Restum98	PCB	1	P1 1.0-1.0 to F1-2	116, 110	69, 55	0.55	340, 304	223, 182	0.63	table 9	80.3	12.5	0.16	table 7 wk 6
Restum98	PCB	0.25	F1-1 0.25-0.25 to F2	116, 106	128, 109	1.07	380, 326	361, 291	0.92	table 10	73	58.3	0.80	table 7 wk 6
Restum98	PCB	0.5	F1-1 0.5-0.5 to F2	116, 106	--, 45	0.42	380, 326	--, 177	0.54	table 10	73	13.3	0.18	table 7 wk 6
Restum98	PCB	1	F1-1 1.0-1.0 to F2							table 10	73	0	0.00	table 7 wk 6
Halbrok99	A1260	0.52	Diet C				328	333	1.02	table 2	63.5	50	0.79	table 2
Halbrok99	A1260	1.01	Diet D				328	307	0.94	table 2	63.5	78.9	1.24	table 2
Halbrok99	A1260	1.36	Diet E				328	295	0.90	table 2	63.5	100	1.57	table 2
Brunstm01	A50	0.77	A50 low							table 3				
Brunstm01	A50	2.31	A50 high							table 3				
Brunstm01	A50	0.77	A50 low	70	48	0.69	258	173	0.67	table 5, fig 2	73	36	0.49	text p 2322
Brunstm01	A50	2.31	A50 high							table 5	73	0	0.00	text p 2322
Kakela02	PCB	0.36	Baltic herring	63, 58	55, 52	0.89	566, 505	501, 439	0.88	table 3				
Kakela02	A1242	2.88	Smelt PCB	63, 58	49, 47	0.80	566, 505	573, 481	0.98	table 3				

Table 7. Summary of Chicken PCB Studies and Relative Responses

Lead author Date	Chemical	Dietary conc. mg/kg fw	Food ingestion kg/kgbw fw	Dose mg/kg-d	Exposure duration wk	Yolk conc. mg/kg fw	Whole egg conc. mg/kg fw	Egg conc. source	Control # or %	Productivity Treatment # or %	RR ratio	Productivity source	Control %	Fertility Treatment %	RR ratio	Fertility source
Briggs72	A1242	20	0.067	1.34	6											
Briggs72	A1242	50	0.067	3.35	6											
Briggs72	A1242	20	0.067	1.34	6											
Briggs72	A1242	50	0.067	3.35	6											
Britton73	A1242	5	0.067	0.34	6	1.7	0.62	table 3 wk 6	61	56	0.92	table 1 wk 6				
Britton73	A1242	10	0.067	0.67	6	3.7	1.35	table 3 wk 6	61	22	0.36	table 1 wk 6				
Britton73	A1242	20	0.067	1.34	6	6.2	2.26	table 3 wk 6	61	25	0.41	table 1 wk 6				
Britton73	A1242	40	0.067	2.68	6	7.7	2.80	table 3 wk 6	61	47	0.77	table 1 wk 6				
Britton73	A1242	80	0.067	5.36	6	27.5	10.01	table 3 wk 6	61	55	0.90	table 1 wk 6				
Platonw73	A1254	5	0.067	0.34	14		5.5	fig 4 max. wk 12	82.7	72	0.87	text p 343 wk 1-14	85.5	83.6	0.98	text p 344 wk 1-14
Platonw73	A1254	5	0.067	0.34	39		7.5	fig 4 max. wk 26	72	57.5	0.80	text p 343 wk 26-39	85	63.3	0.74	fig 2 wk 34-39
Platonw73	A1254	50	0.067	3.35	14		50	fig 4 max. wk 12	82.7	62.2	0.75	text p 343 wk 1-14	85.5	89.9	1.05	text p 344 wk 1-14
Tumas73	A1254	50	0.11	5.50	6	100	36.40	fig 2 wk 3	8.6	8.77	1.02	table 1 wk 1-6	92.3	97.2	1.05	table 1 wk 1-6
Lillie/Cecil74	A1221	20	0.0649	1.30	9		<1	Cecil fig 4 wk 9	79.4	79.3	1.00	Lillie table 1 wk 0-9				
Lillie/Cecil74	A1232	20	0.067	1.34	9		2.5	Cecil fig 4 wk 9	79.4	71.9	0.91	Lillie table 1 wk 0-9				
Lillie/Cecil74	A1242	2	0.0615	0.12	9				79.4	75.5	0.95	Lillie table 1 wk 0-9				
Lillie/Cecil74	A1242	20	0.0605	1.21	9		14	Cecil fig 4 wk 9	79.4	67.5	0.85	Lillie table 1 wk 0-9				
Lillie/Cecil74	A1248	2	0.0623	0.12	9				79.4	76.9	0.97	Lillie table 1 wk 0-9				
Lillie/Cecil74	A1248	20	0.0607	1.21	9		10	Cecil fig 4 wk 9	79.4	67.5	0.85	Lillie table 1 wk 0-9				
Lillie/Cecil74	A1254	2	0.0636	0.13	9				79.4	77.1	0.97	Lillie table 1 wk 0-9				
Lillie/Cecil74	A1254	20	0.061	1.22	9		12	Cecil fig 4 wk 9	79.4	71.3	0.90	Lillie table 1 wk 0-9				
Lillie/Cecil74	A1268	20	0.0641	1.28	9		23	Cecil fig 4 wk 9	79.4	74.4	0.94	Lillie table 1 wk 0-9				
Lillie75	A1232	10	0.067	0.67	8											
Lillie75	A1232	20	0.067	1.34	8											
Lillie75	A1242	5	0.067	0.34	8											
Lillie75	A1242	10	0.067	0.67	8											
Lillie75	A1242	20	0.067	1.34	8											
Lillie75	A1248	5	0.067	0.34	8											
Lillie75	A1248	10	0.067	0.67	8											
Lillie75	A1248	20	0.067	1.34	8											
Scott77	A1248	0.5	0.067	0.03	8		0.22	table 1 wk 8	74.5	74	0.99	table 3 wk 8				
Scott77	A1248	1	0.067	0.07	8		0.41	table 1 wk 8	74.5	76.6	1.03	table 3 wk 8				
Scott77	A1248	10	0.067	0.67	8		3	table 1 wk 8	74.5	68.7	0.92	table 3 wk 8				
Scott77	A1248	20	0.067	1.34	8		7	table 1 wk 8	74.5	64.8	0.87	table 3 wk 8				
Summer96	PCB	0.8	0.0553	0.04	8		4	96b table 1 wk 6-10	54	74	1.37	96a table 5 wk 6-10	67	66.6	0.99	96a table 6 wk 6-10
Summer96	PCB	6.6	0.0548	0.36	8		26	96b table 1 wk 6-10	54	88	1.63	96a table 5 wk 6-10	67	85.7	1.28	96a table 6 wk 6-10
Gould97	A1242	yolk inject				0.067	0.02	table 1								
Gould97	A1242	yolk inject				0.67	0.24	table 1								
Gould97	A1242	yolk inject				6.7	2.44	table 1								
Gould97	A1254	yolk inject				0.067	0.02	table 1								
Gould97	A1254	yolk inject				0.67	0.24	table 1								
Gould97	A1254	yolk inject				6.7	2.44	table 1								

Notes:
Default Food ingestion rate - 0.067 kg feed/kgbw-d white leghorn hen (Medway and Kare 1959)
Whole egg conc. = 0.364 yolk conc. (Sotherland and Rahn 1987)
RR - relative response = treatment response / control response; Normality = 1 - deformity
Tumas73 - Dietary conc. is mg/l water conc; Food ingestion rate is l/kgbw-d water ingestion = 0.177 l/hen/d / 1.61 kgbw/hen (p. 314, 315)
Lillie/Cecil74 - Food consumption = treatment food/hen-d (Lillie table 2 wk 0-9) / 1.953 kg mean initial hen bodyweight (Lillie p 727)
Lillie75 - Normality = 100 - % abnormal embryos of fertile eggs
Summer96 - Food ingestion rate - mean for wk 3-10 (96a table 4); Chick deformity recalculated from 96b table 5 (replace rounded percentages)
Gould97 - Yolk injection on day 0 of incubation. Treatment "chick" bodyweight is % difference in 17-d embryo bodyweight compared to control

Table 7. Summary of Chicken PCB Studies and Relative Responses

Lead author Date	Chemical	Dietary conc. mg/kg fw	Hatchability Control %	Hatchability Treatment %	Hatchability RR ratio	Hatchability source	Chick Bodyweight Control g	Chick Bodyweight Treatment g	Chick Bodyweight RR ratio	Bodyweight source	Chick Survival Control %	Chick Survival Treatment %	Chick Survival RR ratio	Survival source	Chick Normality (1 - defomity) Control %	Chick Normality (1 - defomity) Treatment %	Chick Normality (1 - defomity) RR ratio
Briggs72	A1242	20	68.9	7.2	0.10	table 1 wk 6 leghorn											
Briggs72	A1242	50	68.9	0	0.00	table 1 wk 6 leghorn											
Briggs72	A1242	20	65.5	6.2	0.09	table 1 wk 6 broiler											
Briggs72	A1242	50	65.5	4.5	0.07	table 1 wk 6 broiler											
Britton73	A1242	5	91	94	1.03	table 3 wk 6											
Britton73	A1242	10	91	75	0.82	table 3 wk 6											
Britton73	A1242	20	91	50	0.55	table 3 wk 6											
Britton73	A1242	40	91	0	0.00	table 3 wk 6											
Britton73	A1242	80	91	0	0.00	table 3 wk 6											
Platonw73	A1254	5	90	90	1.00	text p 344 wk 1-14											
Platonw73	A1254	5	90	90	1.00	text p 344, wk 1-39											
Platonw73	A1254	50	90	0	0.00	text p 344 wk 2-14											
Tumas73	A1254	50	84.7	0	0.00	table 1 wk 3-6											
Lillie/Cecil74	A1221	20	93.7	93.2	0.99	Lillie table 3 wk 0-9	163	159	0.98	Lillie table 4 wk 6-	98.4	98.3	1.00	Lillie table 4 wk 6-9			
Lillie/Cecil74	A1232	20	92.4	40	0.43	Cecil fig 1 wk 8	163	139	0.85	Lillie table 4 wk 6-	98.4	91.9	0.93	Lillie table 4 wk 6-9			
Lillie/Cecil74	A1242	2	93.7	92.2	0.98	Lillie table 3 wk 0-9	163	160	0.98	Lillie table 4 wk 6-	98.4	97.1	0.99	Lillie table 4 wk 6-9			
Lillie/Cecil74	A1242	20	92.4	9	0.10	Cecil fig 1 wk 8	163	115	0.71	Lillie table 4 wk 6-	98.4	91.7	0.93	Lillie table 4 wk 6-9			
Lillie/Cecil74	A1248	2	93.7	92.3	0.99	Lillie table 3 wk 0-9	163	153	0.94	Lillie table 4 wk 6-	98.4	97.5	0.99	Lillie table 4 wk 6-9			
Lillie/Cecil74	A1248	20	92.4	8	0.09	Cecil fig 1 wk 8	163	109	0.67	Lillie table 4 wk 6-	98.4	43.7	0.44	Lillie table 4 wk 6-9			
Lillie/Cecil74	A1254	2	93.7	89.7	0.96	Lillie table 3 wk 0-9	163	151	0.93	Lillie table 4 wk 6-	98.4	98.7	1.00	Lillie table 4 wk 6-9			
Lillie/Cecil74	A1254	20	92.4	68	0.74	Cecil fig 1 wk 8	163	141	0.87	Lillie table 4 wk 6-	98.4	93.7	0.95	Lillie table 4 wk 6-9			
Lillie/Cecil74	A1268	20	93.7	92.2	0.98	Lillie table 3 wk 0-9	163	156	0.96	Lillie table 4 wk 6-	98.4	98.7	1.00	Lillie table 4 wk 6-9			
Lillie75	A1232	10	90	77	0.86	text p 1554 wk 8											
Lillie75	A1232	20	90	51	0.57	text p 1554 wk 8											
Lillie75	A1242	5	91	76	0.84	table 3 wk 4-8									98	92	0.94
Lillie75	A1242	10	90	46	0.51	text p 1554 wk 8									98	91	0.93
Lillie75	A1242	20	90	5	0.06	text p 1554 wk 8									98	88	0.90
Lillie75	A1248	5	91	87	0.96	table 3 wk 4-8									98	98	1.00
Lillie75	A1248	10	90	38	0.42	text p 1554 wk 8									98	95	0.97
Lillie75	A1248	20	90	5	0.06	text p 1554 wk 8									98	87	0.89
Scott77	A1248	0.5	90.5	91.6	1.01	table 4 wk 8											
Scott77	A1248	1	90.5	93.7	1.04	table 4 wk 8											
Scott77	A1248	10	90.5	50	0.55	table 4 wk 8											
Scott77	A1248	20	90.5	2.4	0.03	table 4 wk 8											
Summer96	PCB	0.8	85.8	90	1.05	96b table 2 wk 6-1(	34.49	34.49	1.00	96b table 4 wk 6-10					82.7	76.5	0.93
Summer96	PCB	6.6	85.8	70.2	0.82	96b table 2 wk 6-1(	34.49	37.81	1.10	96b table 4 wk 6-10					82.7	59.9	0.72
Gould97	A1242	yolk inject						+8.4 %	1.08	fig 2 (17-d embryo)							
Gould97	A1242	yolk inject						+6.7 %	1.07	fig 2 (17-d embryo)							
Gould97	A1242	yolk inject						-7.0 %	0.93	fig 2 (17-d embryo)							
Gould97	A1254	yolk inject						+2.8 %	1.03	fig 2 (17-d embryo)							
Gould97	A1254	yolk inject						+2.1 %	1.02	fig 2 (17-d embryo)							
Gould97	A1254	yolk inject						-7.7 %	0.92	fig 2 (17-d embryo)							

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Lead author Date	Chemical	Dietary conc. mg/kg fw	Normality source
Briggs72	A1242	20	
Briggs72	A1242	50	
Briggs72	A1242	20	
Briggs72	A1242	50	
Britton73	A1242	5	
Britton73	A1242	10	
Britton73	A1242	20	
Britton73	A1242	40	
Britton73	A1242	80	
Platonw73	A1254	5	
Platonw73	A1254	5	
Platonw73	A1254	50	
Tumas73	A1254	50	
Lillie/Cecil74	A1221	20	
Lillie/Cecil74	A1232	20	
Lillie/Cecil74	A1242	2	
Lillie/Cecil74	A1242	20	
Lillie/Cecil74	A1248	2	
Lillie/Cecil74	A1248	20	
Lillie/Cecil74	A1254	2	
Lillie/Cecil74	A1254	20	
Lillie/Cecil74	A1268	20	
Lillie75	A1232	10	
Lillie75	A1232	20	
Lillie75	A1242	5	Table 3
Lillie75	A1242	10	Table 3
Lillie75	A1242	20	Table 3
Lillie75	A1248	5	Table 3
Lillie75	A1248	10	Table 3
Lillie75	A1248	20	Table 3
Scott77	A1248	0.5	
Scott77	A1248	1	
Scott77	A1248	10	
Scott77	A1248	20	
Summer96	PCB	0.8	96b table 5 wk 1-10
Summer96	PCB	6.6	96b table 5 wk 1-10
Gould97	A1242	yolk inject	
Gould97	A1242	yolk inject	
Gould97	A1242	yolk inject	
Gould97	A1254	yolk inject	
Gould97	A1254	yolk inject	
Gould97	A1254	yolk inject	